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(54) **Thiazole derivative and leukotriene antagonist containing the same as the effective ingredients.**

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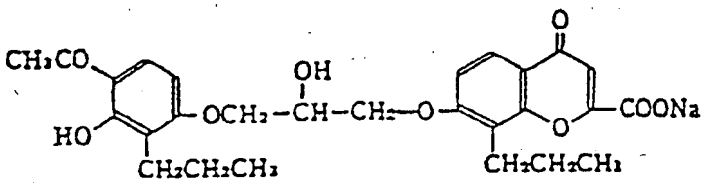
Description

BACKGROUND OF THE INVENTION

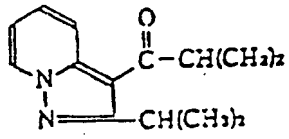
This invention relates to a novel thiazole derivative having leukotriene antagonistic action and a leukotriene antagonist containing the same as the active ingredient.

For prophylaxis or therapy of allergic diseases, there are the method which inhibits liberation of the mediator of anaphylaxis and the method which permits an antagonist to act on the mediator liberated. Disodium cromoglycate [The Merck Index, ninth edition 2585 (1976)] and Tranirast [Journal of Japanese Pharmacology, 74, 699 (1978)] are typical drugs belonging to the former and those belonging to the latter may include drugs antagonistic to hystamine which is one of the mediators of alllergic reactions such as diphenehydramine, chlorophenylamine, astemizole, terfenadine, clemastine, etc., as well known drugs. However, a substance which cannot be antagonized with an anti-hystamine agent, namely SRS (Slow Reacting Substance) has been suggested to be liberated from the lung of a bronchial asthma patient [Progr. Allergy, 6, 539 (1962)], and recently these SRS [leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4)] are comprehensively called SRS [Proc. Natl. Acad. Sci. U.S.A., 76, 4275 (1979) and 77, 2014 (1980); Nature, 285, 104 (1980)] and considered as the important factor participating in human asthma attack [Proc. Natl. Acad. Sci. U.S.A., 80, 1712 (1983)].

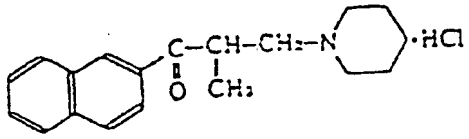
Some leukotriene antagonists have been known in patents or literatures. For example, there have been known FPL-55712 [Agents and Actions, 9, 133 (1979)] represented by the following formula:



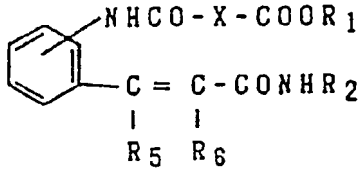
KC-404 [Jap. J. Pharm., 33, 267 (1983)] represented by the following formula:



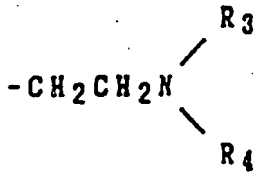
KZ-111 [Chem. Abst, registration number 72637-30-0] represented by the following formula:



and the compound represented by the following formula (U.S. Patent No. 4,296,129):

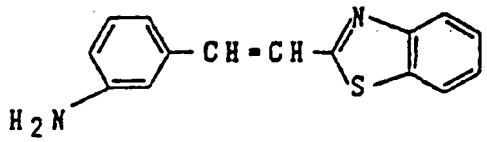


wherein R_1 represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms or a group represented by the following formula:

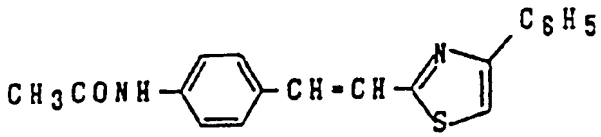


(wherein R_3 and R_4 each represent an alkyl group having 1 to 3 carbon atoms); R_2 represents an alkyl group having 8 to 15 carbon atoms or a cycloalkyl group having 6 to 12 carbon atoms; R_5 and R_6 each represent a hydrogen atom or a methyl group. However, none of these have been clinically applied.

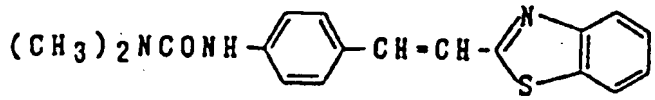
On the other hand, of the thiazole derivatives, as the compounds in which the 2-position of thiazole and the phenyl group are bonded through 2 to 4 atoms, there have been known a large number of compounds such as the compound (Japanese Unexamine Patent Publication No. 22460/1973) represented by the formula:



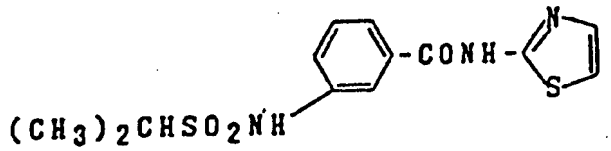
the compound represented by the following formula [Farmaco. Ed. Sci, 21, 740 (1966)]:



the compound represented by the following formula (German Patent No. 31 48 291):



and the compound represented by the following formula (Japanese Unexamined Patent Publication No. 16871/1984):

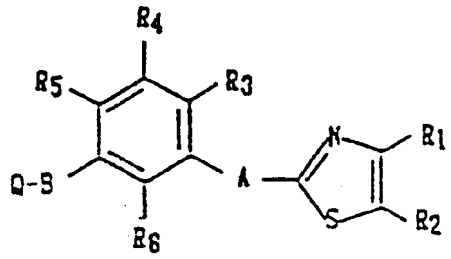


However, in any of these literatures or patents, nothing is mentioned about the leukotriene antagonistic action.

The present inventors have sought after compounds having antagonistic action to leukotriene and effective as the therapeutical medicine for various diseases caused by leukotriene, and consequently found that a novel thiazole derivative has excellent leukotriene antagonistic action to accomplish the present invention.

SUMMARY OF THE INVENTION

The thiazole derivative of the present invention is a compound represented by the following formula (I):



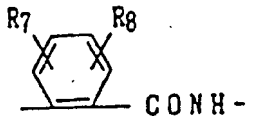
(I)

wherein R_1 and R_2 each independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a lower alkoxycarbonyl group or a substituted or unsubstituted phenyl group or taken together represent a tetramethylene group corresponding to a fused cyclohexane ring or a butadienylene group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group, a lower alkoxycarbonyl group or an alkyl group having 1 to 3 carbon atoms corresponding to a fused benzene ring; R_3, R_4, R_5 and R_6 each independently represent a hydrogen atom, a hydroxyl group, a lower alkoxy group, an alkyl group having 1 to 3 carbon atoms or a halogen atom; A represents a linking group having 2 to 4 chain members; B represents a linking group having 2 to 5 chain members; and Q represents a carboxyl group, a lower alkoxy group, a hydroxyl group, an alkoxycarbonyl group having 2 to 6 carbon atoms or a 5-tetrazolyl group.

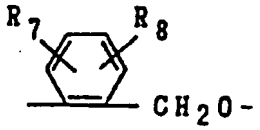
DETAILED DESCRIPTION OF THE INVENTION

In the above formula (I), the alkyl group having 1 to 3 carbon atoms may include methyl, ethyl, propyl and isopropyl. The alkyl group having 1 to 8 carbon atoms may include, in addition to the alkyl groups having 1 to 3 carbon atoms as mentioned above, straight and branched aliphatic groups having 4 to 8 carbon atoms such as butyl, isobutyl, sec-butyl, t-butyl, amyl, isoamyl, sec-amyl, sec-isoamyl (1,2-dimethylpropyl), t-amyl (1,1-dimethylpropyl), hexyl, isohexyl (4-methylpentyl), sec-hexyl (1-methylpentyl), 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, heptyl, isoheptyl (5-methylhexyl), 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, isooctyl (6-methylheptyl), sec-octyl (1-methylheptyl) and t-octyl (1,1,3,3-tetramethylbutyl) group, etc. The lower alkoxy group may include straight and branched alkoxy groups having 1 to 3 carbon atoms such as methoxy, ethoxy, propoxy and isopropoxy group, etc. The lower alkoxy carbonyl group may include straight and branched alkoxycarbonyl groups having 2 to 4 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl group. The alkoxy carbonyl group having 2 to 6 carbon atoms may include, in addition to the lower alkoxycarbonyl group as mentioned above, alkoxycarbonyl groups having 5 to 6 carbon atoms such as butoxycarbonyl group and amyloxycarbonyl group and isomer-substituted groups of these. Examples of the halogen atom may include fluorine atom, chlorine atom, bromine atom and iodine atom. As the substituent on the substituted phenyl group in the definition of R_1 and R_2, there may be employed, for example, the alkyl group having 1 to 3 carbon atoms, lower alkoxy group, lower alkoxycarbonyl group and halogen atom as mentioned above. As the linking group in the definition of A, any group having 2 to 4 atoms as the chain member constituting the linking group may be used, but it should particularly preferably contain carbon atom, oxygen atom, and nitrogen atom. Examples of such a linking group may include -CH=CH-, $-CH_2CH_2-$, $-OCH_2-$, $-NHCH_2-$, -CONH-, -CH=CH-CONH-, $-CH_2OCH_2-$, more preferably -CH=CH-, $-CH_2CH_2-$. As the linking group in the definition of B, any group having 2 to 5 atoms in the chain group constituting the linking group may be used, but it should particularly preferably contain carbon atom, oxygen atom and nitrogen

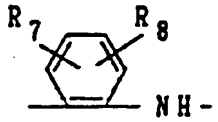
atom. Examples of such a linking group may include
$-(CH_2)_n-CONH-$ (wherein n represents an integer of 0-3),
$-(CH_2)_n-NH-$ (wherein n represents an integer of 1-4),
$-(CH_2)_n-O-$ (wherein n represents an integer of 1-4),
$-(CH_2)_n-$ (wherein n represents an integer of 2-5),



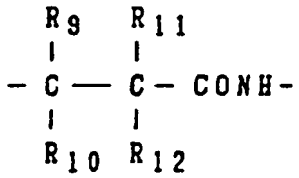
(wherein R_7 and R_8 each independently represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms as defined above),



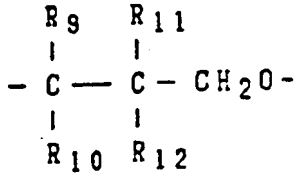
(wherein R_7 and R_8 have the same meanings as defined above),



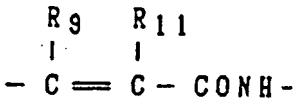
(wherein R_7 and R_8 have the same meanings as defined above),



(wherein R_9, R_{10}, R_{11} and R_{12} each independently represent a hydrogen atom, a phenyl group or an alkyl group having 1 to 6 carbon atoms),

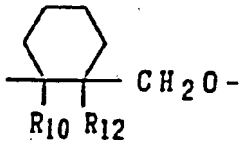


(wherein R_9, R_{10}, R_{11} and R_{12} have the same meanings as defined above),

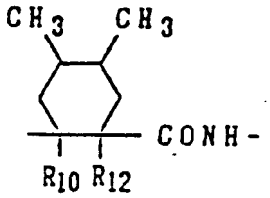


(wherein R_9 and R_{11} have the same meanings as defined above),

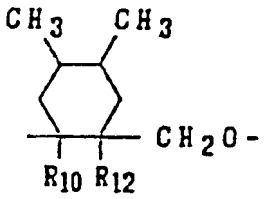
(wherein R_{10} and R_{12} have the same meanings as defined above),



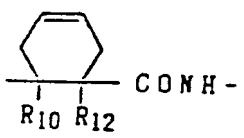
(wherein R_{10} and R_{12} have the same meanings as defined above),



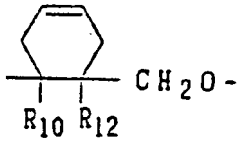
(wherein R_{10} and R_{12} have the same meanings as defined above),



(wherein R_{10} and R_{12} have the same meanings as defined above),

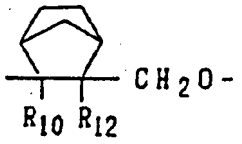


(wherein R_{10} and R_{12} have the same meanings as defined above),

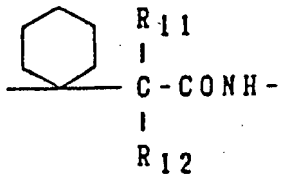


(wherein R_{10} and R_{12} have the same meanings as defined above),

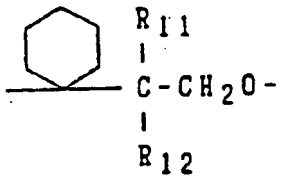
(wherein R_{10} and R_{12} have the same meanings as defined above),



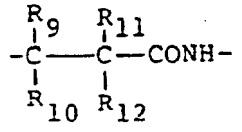
(wherein R_{10} and R_{12} have the same meanings as defined above),



(wherein R_{11} and R_{12} have the same meanings as defined above),



(wherein R_{11} and R_{12} have the same meanings as defined above), more preferably

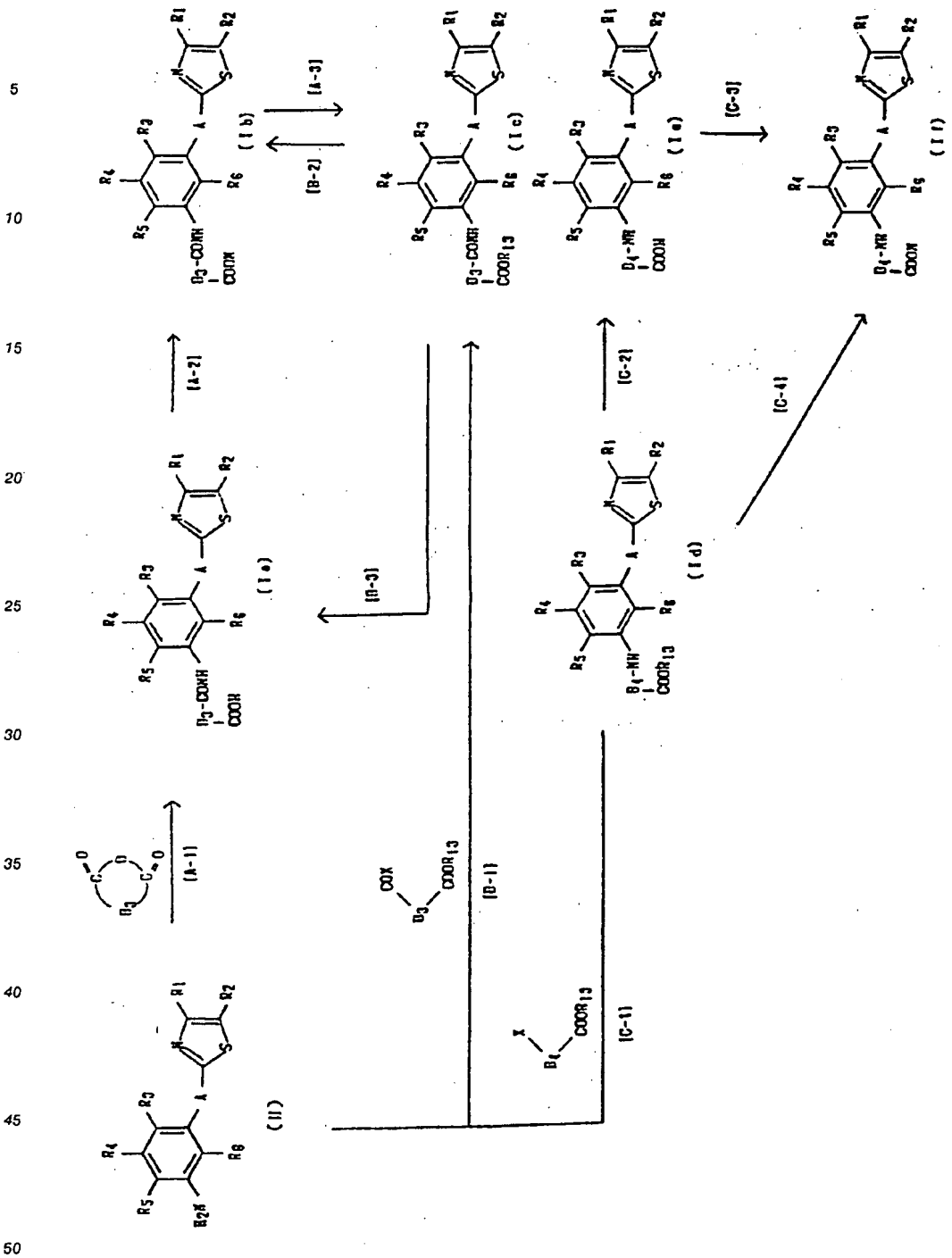


(wherein R_{11} and R_{12} each represent a hydrogen atom and R_9 and R_{10} each independently represent an alkyl group having 1 to 6 carbon atoms).

The thiazole derivative of the present invention is not limited to a specific isomer, but includes all of geometric isomers, steric isomers, optical isomers and their mixtures such as racemic mixture.

The thiazole derivative of the present invention can be synthesized according to various methods.

For example, in the above formula (I), the compound wherein the linking group B is bonded through a nitrogen atom to the benzene ring can be synthesized according to the synthetic routes [A]-[C].



In the synthetic routes, R_1, R_2, R_3, R_4, R_5, R_6 and A have the same meanings as defined above, B_3 represents a direct bond or a linking group having 1 to 3 chain members, B_4 represents a linking group having 1 to 4 chain members, M represents an alkali metal atom, X represents a halogen atom and R_{13} represents an alkyl group having 1 to 5 carbon atoms.

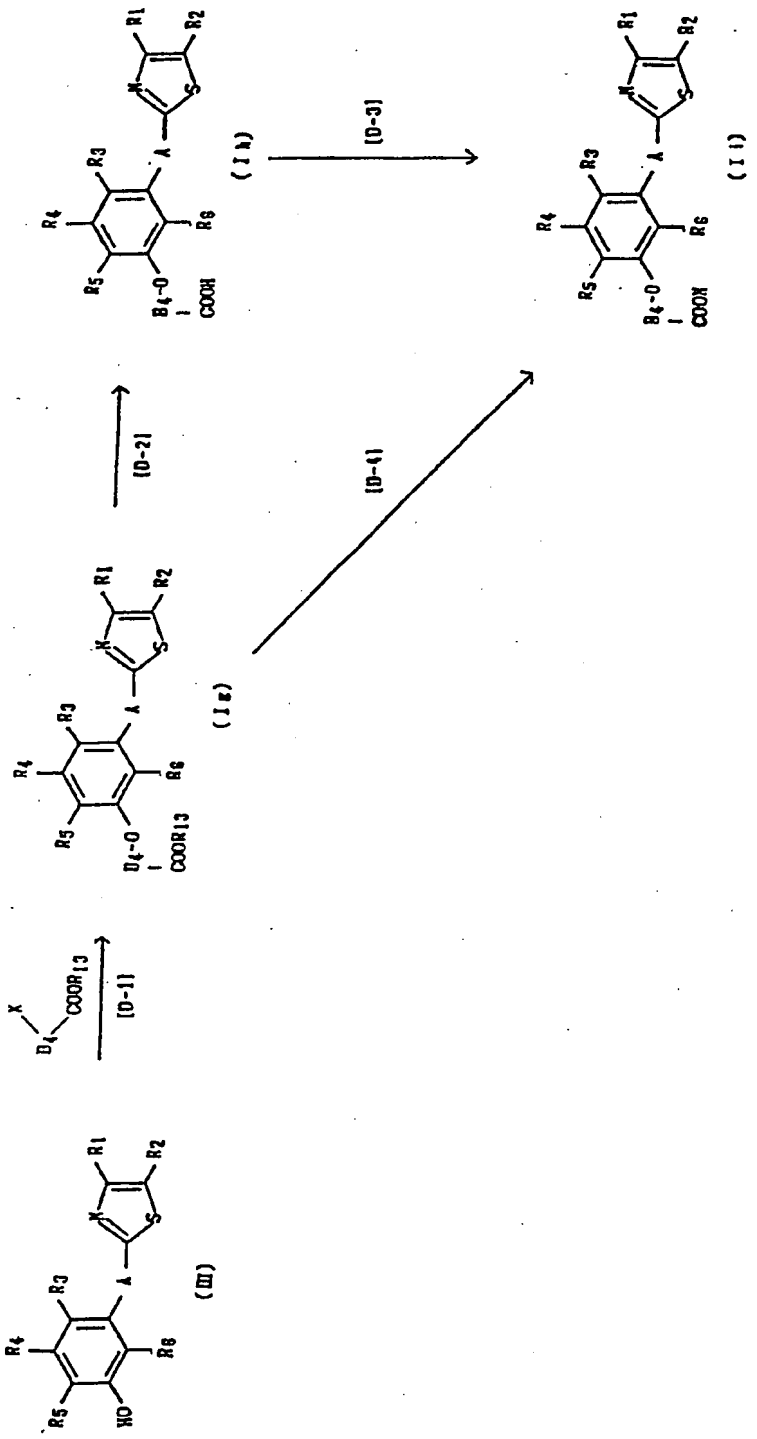
The aniline derivative (II) used as the starting material can be synthesized according to the known method [Tetrahedron Letters, 25, 839 (1984)].

In the synthetic route [A], the aniline derivative (II) is allowed to react with 0.8 to 2 equal amounts of a cyclic acid anhydride to obtain the compound (Ia) (step [A-1]). As the reaction solvent, there may be employed aromatic hydrocarbons such as toluene, benzene, etc.; ether type solvent such as ethyl ether, dioxane, tetrahydrofuran, etc.; halogenated hydrocarbons such as chloroform, dichloromethane, etc. This reaction may be practiced at a temperature from under ice-cooling to the boiling point of the solvent, particularly preferably from room temperature to 60 °C. The compound (Ia) can be converted to an alkali metal salt (Ib) by the reaction with a carbonate, a hydrogen carbonate or a hydroxide of the corresponding alkali metal in a hydrous alcoholic solvent (step [A-2]). Further, the compound (Ib) can be allowed to react with 1 to 3 equivalents of an alkylating agent such as an alkyl halide or an alkyl sulfonate, etc., in a non-protonic polar solvent such as dimethyl sulfoxide, dimethylformamide, hexamethylphosphoramide triamide, etc., at 0 to 100 °C to be alkylated and converted to a carboxylic acid ester (Ic) (step [A-3]).

In the synthetic route [B], the compound (II) can be acylated by the reaction with a carboxylic acid monoester monohalide in the presence of an organic base such as pyridine, triethylamine, etc., or an inorganic base such as potassium carbonate, sodium hydrogen carbonate, etc., at 0-100 °C to synthesize the compound (Ic) (step [B-1]). As the reaction solvent, there may be used aromatic hydrocarbons, ether type solvents, halogenated hydrocarbons or non-protonic polar solvents. The compound (Ic) can be hydrolyzed in a conventional manner in a hydrous alcoholic solvent with an alkali metal type inorganic base such as sodium hydroxide, potassium carbonate, etc., to be readily converted to the compound (Ib) (step [B-2]). Also, after the above hydrolysis, the product can be treated with a mineral acid to obtain a free carboxylic acid (Ia) (step [B-3]).

In the synthetic route [C], the compound (II) can be allowed to react with a ω-halocarboxylic acid ester in the presence of an organic base such as triethylamine, pyridine, etc., in an aromatic hydrocarbon type, ether type or halogenated hydrocarbon type solvent at a temperature from 0 °C to the boiling point of the solvent to effect N-alkylation and result in synthesis of the compound (Id) (step [C-1]). The compound (Ie) can be synthesized according to the same method as in the step [B-3] (step [C-2]), and the compound (If) can be synthesized in the same manner as in the step [A-2] or the step [B-2] (step [C-3], step [C-4]).

In the above formula (I), the compound wherein the linking group B is bonded through an oxygen atom to the benzene ring can be synthesized according to the synthetic route [D] shown below.

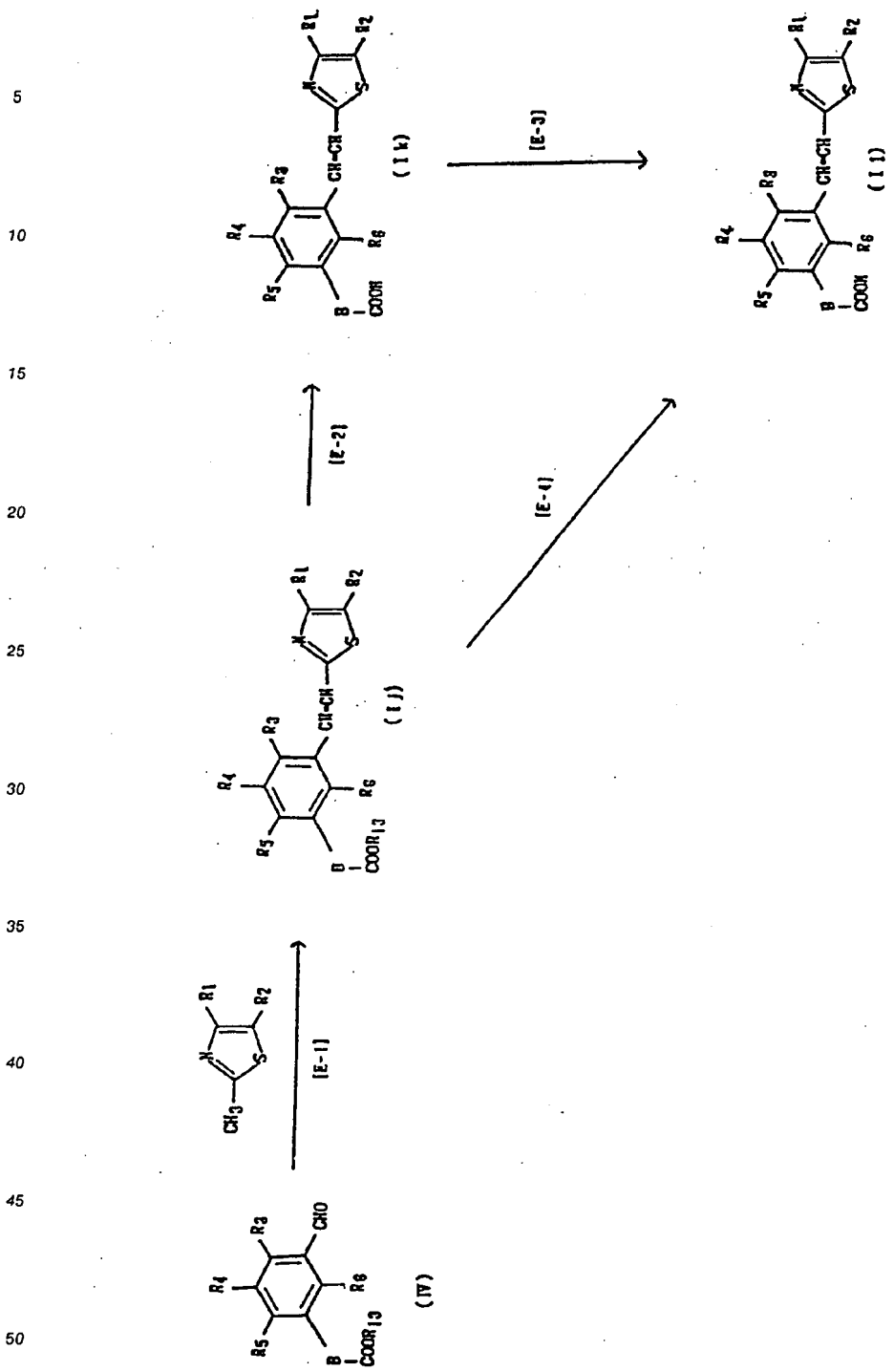


In the above synthetic route, R_1, R_2, R_3, R_4, R_5, R_6, R_{13}, A, B_4, M and X have the same meaning as defined above.

The phenol derivative (III) used as the starting material can be synthesized according to the known method [Journal of Medicinal Chemistry, 25, 1378 (1982)].

By O-alkylation of the compound (III) with a ω-halocarboxylic acid ester in a solvent of ketone type such as acetone, methyl ethyl ketone, etc., or alcohol type, in the presence of an inorganic base such as potassium carbonate, sodium hydrogen carbonate, etc., at a temperature from 0 °C to the boiling point of the solvent, the phenylether compound (Ig) can be synthesized (step [D-1]). The compound (Ih) can be obtained from the compound (Ig) similarly as in the step [B-2] (step [D-2]), and the compound (Ii) can be obtained from the compound (Ih) according to the same method as in the step [A-2] (step [D-3]), or from the compound (Ig) in the same manner as in the step [B-2] (step [D-4]).

In the above formula (I), the compound when the linking group A is a vinylene group can be synthesized according to the synthetic route [E] shown below.



In the above synthetic route, R_1, R_2, R_3, R_4, R_5, R_6, R_{13} B and M have the same meanings as defined above. The benzaldehyde derivative [IV] used as the starting material can be synthesized according to the known method [Journal of Medicinal Chemistry, 25, 1378 (1982)].

The compound (Ij) can be obtained according to the dehydrating condensation reaction by heating the benzaldehyde derivative (IV) and a 2-methylthiazole in acetic anhydride under nitrogen gas stream to 100-

200 °C (step [E-1]). Hydrolysis of the compound (Ij) in the same manner as in the step [B-3] gives the compound (Ik) (step [E-2]). From the compound (Ik), an alkali metal salt (II) can be obtained in the same manner as in the step [A-2] (step [E-3]). The alkali metal salt (II) can be obtained also by treating similarly the compound (Ij) as in the step [B-2] (step [E-4]).

The compound (I) or the present invention is characterized by having a marked leukotriene antagonistic action.

More specifically, when the antagonistic action to SRS was tested in vitro by use of an extirpated ileum of a guinea pig for the compound of the present invention, it has been found to have a selective antagonistic action for SRS even at an extremely low concentration. When further detailed LTD_4 antagonistic test was conducted by use of a guinea pig for some of the compounds of the present invention which have exhibited strong action in vitro test, it has been found that they can inhibit remarkably the asthmatic symptoms induced by LTD_4.

The leukotriene antagonist of the present invention contains the compound represented by the above formula (I) or its pharmaceutically acceptable salt as the active ingredient together with a solid or liquid carrier or diluent for medicine, namely additives such as excepients, stabilizers, etc. When the compound (I) has a carboxylic group, preferable salts are non-toxic salts which are pharmaceutically acceptable such as alkali metal salts and alkaline earth metal salts such as sodium salts, pottasium salts, magnesium salts, calcium salts or aluminum salts. It is similarly preferable to use adequate non-toxic amine salts such as ammonium salts, lower-alkylamine [e.g. triethylamine] salts, hydroxy lower-alkylamine [e.g. 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tris(hydroxymethyl)aminomethane or N-methyl-D-glucamine] salts, cycloalkylamine [e.g. dicyclohexylamine] salts, benzylamine [e.g. N,N'-dibenzylethylenediamine] salts and dibenzylamine salts. In view of the basicity of the thiazole ring of the compound (I) of the present invention, preferable salts may include non-toxic salts such as hydrochlorides, methanesulfonates, hydrobromides, sulfates, phosphates, fumarates, succinates, etc. These salts are water-soluble and hence most preferable when used for injections. In said leukotriene antagonist, the proportion of the active ingredient to the carrier component in therapy may be variable between 1 wt.% to 90 wt.%. The leukotriene antagonist may be administered orally in the dosage form such as granules, fine particles, powders, tablets, hard capsules, soft capsules, syrup, emulsion, suspension or solution, or alternatively administered intravenously, intramascularly or subcutaneously as injections. Also, it can be used as topical administration preparation to rectum, nose, eye, lung in the dosage form such as suppository, collunarium, eye drops or inhalent. Further, it can be used in the form of powder for injection which is to be formulated when used. It is possible to use an organic or inorganic, solid or liquid carrier or diluent for medicine suitable for oral, rectal, parenteral or local administration for preparation of the leukotriene antagonist of the present invention. Examples of the excepient to be used in preparation of a solid preparation may include lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate, etc. Liquid preparations for oral administration, namely, emulsion, syrup, suspension, solution, etc., contain inert diluents generally employed such as water or vegetable oils, etc. These preparations can contain auxiliary agents other than inert diluents such as humectants, suspension aids, sweeteners, aromatics, colorants or preservatives. It may also be formulated into a liquid preparation which is contained in capsules of absorbable substances such as gelatin. As the solvent or suspending agent to be used for production of preparations for parentheral administration, namely injections, suppositories, collunarium, eye drops, inhalent, etc., there may be employed, for example, water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin, etc. As the base to be used for suppository, there may be included, for example, cacao fat, emulsified cacao fat, laurine fat, Witepp sol, etc. The preparations can be prepared according to conventional methods.

The clinical dose, when used by oral administration, may be generally 0.01 to 1000 mg/day as the compound of the present invention for human adult, preferably 0.01 to 100 mg, but it is more preferable to increase or decrease suitably the dose depending on the age, condition of disease and symptoms. The above mentioned dose per day of the leukotriene antagonist may be administered once per day or in 2 or 3 divided doses per day at suitable intervals, or intermittently.

On the other hand, when used as an injection, it is preferable to administer continuously or intermittently 0.001 to 100 mg/administration as the compound of the present invention to human adult.

According to the present invention, a novel thiazole derivative having remarkable leukotriene antagonistic action can be provided. Said thiazole derivative is useful as the leukotriene antagonist for prophylaxis and therapy of various diseases in which leukotriene participates.

The present invention is described in more detail by referring to Synthesis examples, Examples and Test examples, but these are not intended to limit the scope of the present invention at all. In Synthesis examples and Examples, the symbols of "IR", "TLC", "NMR" and "MS" represent "infrared-absorption spectrum", "thin layer chromatography", "nuclear magnetic resonance spectrum" and "mass analysis",

respectively, the proportion of the solvent written at the site of separation by chromatography indicating volume ratio, the solvent in the parenthesis of "TLC" indicating a developing solvent, "IR" being measured according to the KBr tablet method unless otherwise specifically noted, and the solvent in the parenthesis of "NMR" indicating the measurement solvent.

Synthesis example 1

Synthesis of 4-isopropyl-2-methylthiazole

To a solution of 25 g of 3-methyl-2-butanone dissolved in 174 ml of methanol, 15.8 ml of bromine was added dropwise while temperature of the reaction mixture was maintained within the range of 0 to 5 °C, and further the mixture was stirred at 10 °C for 1 hour. Then, 87 ml of water was added and the mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was extracted with ethyl ether, the extract was washed with 10% aqueous potassium carbonate solution and dried over calcium chloride, followed by evaporation of the solvent to give 53.2 g of a crude product of 1-bromo-3-methyl-4-butanone as colorless liquid. Further, without purification, 43.2 g of the above bromoketone was dissolved in 100 ml of ethanol and the solution was added at room temperature to a solution of 19.7 g of thioacetamide dissolved in 150 ml of ethanol. After the reaction was completed by refluxing for 2.5 hours, ethanol was evaporated under reduced pressure and the residue was ice-cooled to precipitate crystals. The crystals are washed with ethyl ether, poured into 250 ml of an aqueous saturated sodium hydrogen carbonate solution, free bases were extracted with n-hexane, followed by drying over anhydrous magnesium sulfate and concentration under reduced pressure to give 27.1 g (yield 73%) of the title compound as pale brown liquid.

IR (film): ν = 2950, 1510, 1450, 1165, 730 cm^{-1}

NMR ($CDCl_3$): δ = 1.30(6H,d), 2.68(3H,s), 3.07(1H,m), 6.67(1H,s)

Synthesis example 2

Synthesis of 4-isopropyl-2-(trans-3-nitrostyryl) thiazole

To 11.3 ml of acetic anhydride were added 29.0 g of 3-nitrobenzaldehyde and 27.1 g of 4-isopropyl-2-methylthiazole and the reaction was carried out under nitrogen gas stream at 170 °C for 23 hours. After completion of the reaction, low boiling materials were evaporated under reduced pressure and the residue was recrystallized from ethyl ether-n-hexane to give 16.8 g (yield 32%) of the title compound as yellowish white crystals.

NMR ($CDCl_3$): δ = 1.34(6H,d), 3.12(1H,m), 6.86(1H,s), 7.2-8.4(6H,m)

IR: ν = 1625, 1590, 1435, 1305, 1210, 945, 770 cm^{-1}

Synthesis example 3

Synthesis of 2-(3-nitrophenyl)methoxymethylbenzothiazole

A mixture of 1.60 g of 3-nitrobenzyl chloride, 1.3 g of 2-hydroxymethylbenzothiazole and 0.54 g of potassium carbonate in 20 ml of acetone was stirred at room temperature for 1.5 hours and then refluxed for 30 minutes. After evaporation of acetone under reduced pressure, the residue was dissolved in ethyl acetate, washed with water and dried over magnesium sulfate, followed by evaporation of the solvent under reduced pressure. The residue was purified through a silica gel column chromatography by use of ethyl ether-n-hexane to obtain 1.7 g (yield 73%) of the title compound.

IR: ν = 1520, 1340, 1090, 800, 766, 725 cm^{-1}

NMR ($CDCl_3$): δ = 4.65(2H,s), 4.90(2H,s), 7.1-8.2 (8H,m)

Synthesis example 4

Synthesis of 2-[2-(3-hydroxyphenyl)ethyl]benzothiazole

A mixture of 6.0 g of 2-(trans-3-hydroxystyryl) benzothiazole and 0.5 g of 5% palladium-carbon in 80 ml of ethanol was stirred under hydrogen gas stream under normal pressure at 50 to 60 °C for 3 hours. After completion of the reaction, the catalyst was filtered off and the filtrate was evaporated under reduced

pressure to obtain 5.5 g (yield 92%) of the title compound as pale gray crystals.

IR: ν = 3050, 1580, 1480, 1280, 760 cm^{-1}

m.p.: 129-130 °C

Synthesis example 5

Synthesis of 2-(trans-3-hydroxystyryl)-4-ethyl-5-methylthiazole

An amount of 3.0 g of 2-(trans-3-aminostyryl)-4-ethyl-5-methylthiazole was added to 18 ml of 20% hydrochloric acid and to the mixture was added dropwise slowly 3 ml of an aqueous solution of 0.86 g of sodium nitrite while maintaining the inner temperature at 4 to 5 °C. After the mixture was stirred at the above temperature for 1.5 hours, the reaction mixture was added into 50 ml of boiling water over 20 minutes. After the mixture was cooled to room temperature, the precipitates formed were collected by filtration, washed with aqueous saturated sodium hydrogen carbonate solution and with water, followed by drying under reduced pressure. The crude product was washed with toluene and dried under reduced pressure to obtain 2.1 g (yield 70%) of the title compound.

m.p.: 161-162 °C

IR: ν = 1620, 1598, 1575, 1215, 950, 778 cm^{-1}

Synthesis example 6

(1) Synthesis of 2-(trans-3-hydroxystyryl)benzothiazole

A mixture of 25 g of 3-hydroxybenzaldehyde, 36.6 g of 2-methylbenzothiazole, 38.8 ml of acetic anhydride and 7.7 ml of formic acid was heated at 120 °C for 25 hours. The low boiling materials were evaporated together with toluene under reduced pressure, and the residue was added to 150 ml of methanol and refluxed with addition of 3 g of potassium carbonate for 1 hour. After cooled to room temperature, the mixture was filtered and filtrate was concentrated. The crude product formed was washed with methanol and ethyl ether and dried under reduced pressure to obtain 20.6 g (yield 40%) of the title compound.

m.p.: 210-211 °C

IR: ν = 1620, 1570, 1190, 1145, 935, 750 cm^{-1}

(2) The operation similar to (1) was conducted to obtain 2-(trans-3-hydroxystyryl)-4-phenylthiazole (yield 21%).

m.p.: 150-151 °C

IR: ν = 3450, 1580, 1280, 950, 730 cm^{-1}

Synthesis example 7

Synthesis of ethyl 5-(3-cyanophenyl-4-pentenoate

An amount of 0.66 g of 60% sodium hydride was added to 14 ml of anhydrous dimethyl sulfoxide and the mixture was heated under nitrogen gas stream to 75 to 80 °C to form dimsyl anions. After cooled to room temperature, the mixture was added to a solution of 6.3 g of 3-ethoxycarbonylpropyltriphenylphosphonium bromide in 20 ml of anhydrous dimethyl sulfoxide. The mixture was stirred at room temperature for 5 minutes and a solution of 1.5 g of 3-cyanobenzaldehyde in 4 ml of anhydrous dimethyl sulfoxide, followed by stirring at room temperature for 1.5 hours. After completion of the reaction, 5% hydrochloric acid was added to stop the reaction, and the reaction mixture was extracted with toluene. After evaporation of the solvent under reduced pressure, the residue was purified through silica gel column chromatography by use of ethyl ether-n-hexane to obtain 0.94 g (yield 36%) of the title compound as colorless oily product.

IR (film): ν = 1725, 1245, 1180, 1150, 960, 785 cm^{-1}

NMR (CCl_4): δ = 1.25(3H,t), 2.2-2.8(4H,m), 4.09(2H,q), 6.2-6.6(2H,m), 7.3-7.7(4H,m)

Synthesis example 8

Synthesis of ethyl 5-(3-formylphenyl)pentanoate

An amount of 660 mg of ethyl 5-(3-cyanophenyl)-4-pentenoate and 60 mg of 5% palladium-carbon were added into 6 ml of ethanol and catalytic reduction was carried out under hydrogen gas stream at room temperature for 18 hours. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure and 600 mg of the crude product was used for the subsequent reaction.

Into a suspension of 986 mg of anhydrous stannous chloride in anhydrous ethyl ether was introduced hydrogen chloride gas for 2 minutes to provide a uniform solution. Next, 600 mg of the above saturated carboxylic acid ester dissolved in 4 ml of ethyl ether was added and hydrogen chloride gas was introduced again for 1 minute, followed by stirring at room temperature for 5 hours. Subsequently, each 5 ml of ethyl ether and water was added and after stirred at room temperature for 1 hour, the organic layer was extracted with toluene. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure and the residue was purified through silica gel column chromatography by use of ethyl ether-n-hexane to give 460 mg (yield 68%) of the title compound as colorless oily product.

IR (film): ν = 1725, 1690, 1440, 1365, 1235, 1180, 1020, 790 cm^{-1}

NMR (CCl_4): δ = 1.20(3H,t), 1.4-1.9(4H,m), 2.0-2.9(4H,m), 4.5(2H,q), 7.2-7.8(4H,m), 9.88(1H,s)

Synthesis example 9

Synthesis of 2-[trans-3-(3-cyanopropylamino) styryl)benzothiazole

To 50 ml of toluene were added 2.02 g of triethylamine and 5.04 g of 2-(trans-3-aminostyryl)-benzothiazole at room temperature, and then 2.96 g of 4-bromobutyronitrile was added to carry out the reaction at 110 °C for 7 hours. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. After evaporation of the solvent under reduced pressure, the residue was purified through silica gel column chromatography by use of ethyl acetate-ethyl ether-n-hexane (2 : 5 : 5) to give 2.55 g (yield 40%) of the title compound as colorless oily product.

m.p.: 97-98 °C

IR: ν = 3400, 2250, 1600, 950, 760 cm^{-1}

Synthesis example 10

Synthesis of 4-isopropyl-2-(trans-3-aminostyryl) thiazole

To a solution of 16.8 g of 4-isopropyl-2-(trans-3-nitrostyryl)thiazole dissolved in 60 ml of ethanol was added a solution of 48.4 g of stannous chloride dihydrate in 60 ml of ethanol and the mixture was refluxed for 1.5 hours. After the reaction mixture was cooled to room temperature, the mixture was adjusted to pH 13 with addition of 30% aqueous sodium hydroxide solution and then the basic portion was extracted with the use of ethyl acetate and dried over magnesium sulfate, followed by evaporation of the solvent under reduced pressure. The solid residue formed was recrystallized from ethyl ether-n-hexane to obtain 7.1 g (yield 47%) of the pale yellowish white title compound.

m.p.: 62-63 °C

IR: ν = 3430, 3300, 1600, 1580, 960, 780, 740 cm^{-1}

NMR ($CDCl_3$): δ = 1.32(6H,d), 2.90-3.4(1H,m), 3.70(2H,s), 6.5-7.3(7H,m)

Synthesis example 11

Synthesis of various thiazole derivatives

By carrying out the treatment similarly as in Synthesis example 10, various thiazole derivatives shown as Nos. 1-32 and 36-38 in Table 1 were obtained.

Synthesis example 12

Synthesis of 2-[2-(3-aminophenyl)ethyl]-4-ethyl-5-methylthiazole

An amount of 1.0 g of 2-(3-aminostyryl)-4-ethyl-5-methylthiazole and 200 mg of 5% palladium-carbon were added to 20 ml of ethanol and catalytic reduction was carried out in a hydrogen gas atmosphere at room temperature and normal pressure for 12 hours. After the reaction mixture was filtered, the solvent was evaporated under reduced pressure to give 0.90 g (yield 90%) of the title compound as pale yellow crystals.

m.p.: 64-65 °C

IR: ν = 3410, 1590, 1300, 1120, 950, 760 cm^{-1}

Synthesis example 13

Synthesis of various 2-[2-(3-aminophenyl)ethyl] thiazoles

By carrying out the treatment similarly as in Synthesis example 12, various 2-[2-(3-aminophenyl)ethyl]-thiazoles shown as Nos. 34 and 35 in Table 1 were obtained.

Synthesis example 14

Synthesis of 2-(trans-3-amino-4-hydroxystyryl) benzothiazole

To a solution of 282 mg of 2-(trans-3-amino-4-methoxystyryl)benzothiazoledissolved in 30 ml of dichloromethane was added 380 mg of phosphorous tribromide at 70 °C, and the mixture was gradually returned to room temperature and stirred overnight. After an aqueous saturated sodium, hydrogen carbonate solution was added to the reaction mixture to make it weakly alkaline, the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give 260 mg (yield 97%) of the title compound.

m.p.: 192-193 °C

IR: ν = 3400, 1590, 1510, 1290, 800, 760 cm^{-1}

Synthesis example 15

Synthesis of 2-(trans-3-amino-6-hydroxystyryl) benzothiazole

By carrying out the treatment similarly as in Synthesis example 14, the title compound shown as No. 33 in Table 1 was obtained.

Synthesis example 16

Synthesis of 2-(trans-3-aminostyryl)-5-methoxycarbonylbenzothiazole

To a solvent mixture of 50 ml of dioxane and 30 ml of methanol, 2.0 g of 5-methoxycarbonyl-2-(trans-3-nitrostyryl)benzothiazole was added and, under vigorous stirring, a solution of 0.37 g of calcium chloride in 55 ml of water and 9.8 g of zinc powder were added, followed by refluxing for 2 hours. After cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure, and the solid residue formed was washed with toluene to give 1.4 g (yield 77%) of the title compound.

m.p.: 165-167 °C

IR: ν = 1710, 1630, 1305, 1100, 755 cm^{-1}

Example 1

Synthesis of 2-[trans-3-(cis-3-carboxypropenamide) styryl]benzothiazole (compound No. 1)

To 8 ml of toluene were added 158 mg of 2-(trans-3-aminostyryl)benzothiazole and 71 mg of maleic anhydride, and the mixture was heated at 80 °C for 1 hour. After cooled to room temperature, the crystals formed were collected by filtration and recrystallized from ethanol to give 194 mg (yield 88%) of the yellowish white title compound.

m.p.: 190-191 °C
IR: ν = 1700, 1625, 1550, 1490, 1405, 953 cm^{-1}

Example 2

Synthesis of various anilide carboxylic acids

By carrying out the treatment similarly as in Example 1, the title compounds shown as compounds Nos. 2-165 and 445-448 in Table 2 were obtained.

Example 3

Synthesis of 2-(trans-3-oxalylaminostyryl)-4-phenylthiazole (compound No. 166)

To a suspension of 1.0 g of 2-(trans-3-ethyloxalylaminostyryl)-4-phenylthiazole in 40 ml of dioxane was added, under vigorous stirring, 1 ml of an aqueous 20% potassium hydroxide solution, and hydrolysis was carried out at room temperature for 1 hour. To the reaction mixture was added 20% hydrochloric acid to adjust the pH to 1-2, and the yellow precipitates formed were collected by filtration and washed with ethanol and chloroform, followed by drying under reduced pressure to give 870 mg (yield 94%) of the title compound.

m.p.: 291-292 °C
IR: ν = 1715, 1685, 1590, 1520, 1300, 1180, 740 cm^{-1}

Example 4

Synthesis of various anilidecarboxylic acids

By carrying out the treatment similarly as in Example 3, the title compounds shown as compounds Nos. 167-169 in Table 2 were obtained.

Example 5

Synthesis of 2-[trans-3-(3-carboxypropylamino) styryl]-4-propylthiazole (compound No. 170)

To 20 ml of toluene were added 732 mg of 2-(trans-3-aminostyryl)-4-propylthiazole, 1170 mg of ethyl 4-bromobutyrate and 606 mg of triethylamine, and the reaction was carried out at 100 °C for 21 hours. After the reaction mixture was cooled to room temperature, 10 ml of ethanol and 10 ml of an aqueous 5% sodium hydroxide solution were added and the mixture was stirred at room temperature for 1.5 hours to effect hydrolysis of the ester. After completion of the reaction, ethanol was evaporated under reduced pressure and the residue was adjusted to pH 1-2 with addition of 10% hydrochloric acid, followed by extraction with ethyl ether. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the solid formed was recrystallized from ethyl ether to give 629 mg (yield 64%) of the title compound.

m.p.: 115-116 °C
IR: ν = 1705, 1595, 1480, 1190, 940, 740 cm^{-1}

Example 6

Synthesis of various anilinocarboxylic acid

By carrying out the treatment similarly as in Example 5, the title compounds shown as compounds Nos. 171-182 in Table 2 were obtained.

Example 7

Synthesis of 2-(trans-3-ethyloxalylaminostyryl)-4-phenylthiazole (compound No. 183)

To 30 ml of toluene were added 0.7 g of pyridine and 2.0 g of 2-(trans-3-aminostyryl)-4-phenylthiazole and a solution of 1.1 g of ethyloxalyl chloride in 5 ml of toluene was added dropwise at 0 °C under stirring,

followed by heating at 50 °C for 1.5 hours. The reaction mixture was poured into ice-cold water and crystals formed were collected by filtration and dried, followed by recrystallization from chloroform to give 2.5 g (yield 90%) of the title compound.

m.p.: 193-194 °C

IR: ν = 3325, 1715, 1700, 1300, 730 cm^{-1}

Example 8

Synthesis of various anilidecarboxylic acid esters

By carrying out the treatment similarly as in Example 7, the title compounds shown as compounds Nos. 184-188 in Table 2 were obtained.

Example 9

Synthesis of 2-[trans-3-(cis-3-isoamyloxycarbonylpropenamide)styryl]benzothiazole (compound No. 189)

To 6 ml of hexamethylphosphoric triamide were added 1.0 g of sodium salt of 2-[trans-3-(cis-3-carboxypropenamide)styryl]benzothiazole and 2.13 g of isoamyliodide, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was extracted with toluene in a conventional manner, the extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure, followed by recrystallization of the residue from ethyl ether-toluene to give 616 mg (yield 55%) of the title compound.

m.p.: 82-83 °C

IR: ν = 3400, 1720, 1660, 1580, 1440, 1200, 755 cm^{-1}

Example 10

Synthesis of various anilidecarboxylic acid esters

By carrying out the treatment similarly as in Example 9, the title compounds shown as compounds Nos. 190-195 in Table 2 were obtained.

Example 11

Synthesis of 2-[trans-3-(4-ethoxycarbonyl)butylstyryl]benzothiazole (compound No. 196)

A mixture of 460 mg of ethyl 5-(3-formylphenyl) pentanoate, 322 mg of 2-methylbenzothiazole and 0.11 ml of acetic anhydride was heated under nitrogen gas stream to 170 °C for 30 hours. The reaction mixture was directly purified through silica gel column chromatography by use of ethyl ether-n-hexane to obtain 320 mg (yield 45%) of the title compound as brown oily product.

IR: ν = 1720, 1620, 1485, 1180, 950, 750 cm^{-1}

NMR (CCl_4): δ = 1.25(3H,t), 1.35-2.05(4H,m), 2.01-2.85(4H,m), 4.07(2H,q), 7.05-8.10(10H,m)

Example 12

Synthesis of various 2-(trans-3-alkoxycarbonyl-alkylenestyryl)benzothiazoles

By carrying out the treatment similarly as in Example 11, the title compounds shown as compounds Nos. 197 and 198 in Table 2 were obtained.

Example 13

Synthesis of 2-[trans-3-(3-ethoxycarbonylpropyl) aminostyryl]benzothiazole (compound No. 199)

To 10 ml of toluene were added 1.0 g of 2-(trans-3-aminostyryl)benzothiazole,0.78 g of ethyl 4-bromobutyrate and 0.4 g of triethylamine, and the mixture was stirred at 100 °C for 20 hours. After cooled to room temperature, the mixture was extracted with toluene, dried over anhydrous magnesium sulfate and

then the solvent was evaporated under reduced pressure. The residue was purified through silica gel column chromatography by use of ethyl acetate-n-hexane to obtain 951 mg of the title compound (yield 66%).

m.p.: 68-69 °C

NMR ($CDCl_3$): δ = 1.25(3H,t), 2.0(2H,m), 2.35(2H,t), 3.22(2H,t), 4.23(2H,q), 6.45-8.10(10H,m)

Example 14

Synthesis of various anilinocarboxylic acid esters

By carrying out the treatment similarly as in Example 13, the title compounds shown as compounds Nos. 200-205 in Table 2 were obtained.

Example 15

Synthesis of 2-(trans-3-ethoxycarbonylmethoxystyryl)benzothiazole (compound No. 206)

To 30 ml of acetone were added 200 mg of 2-(trans-3-hydroxystyryl)benzothiazole, 0.11 ml of ethyl bromoacetate and 131 mg of potassium carbonate, and the mixture was refluxed for 4 hours. After cooled to room temperature, the mixture was extracted with ethyl ether, dried over anhydrous magnesium sulfate and then the solvent was evaporated under reduced pressure. After the crude crystals of the residue were washed with ethyl ether and n-hexane, they were dried under reduced pressure to give 207 ml (yield 77%) of the title compound.

m.p.: 150-151 °C

IR: ν = 1720, 1585, 1260, 1190, 1025, 950, 755 cm^{-1}

Example 16

Synthesis of various alkoxycarbonylalkylphenylethers

By carrying out the treatment similarly as in Example 15, the title compounds shown as compounds Nos. 207-212 and 431-433 in Table 2 were obtained.

Example 17

Synthesis of 2-[trans-3-(cis-3-carboxypropenamide) styryl]benzothiazole sodium salt (compound No. 213)

To 350 ml of methanol was added 17.3 g of 2-[trans-3-(cis-3-carboxypropenamide)styryl]benzothiazole and then a solution of 4.1 g of sodium hydrogen carbonate in 75 ml of water, followed by refluxing for 1 hour. The solvent was evaporated under reduced pressure, and the crude crystals of the residue were washed with ethanol and ethyl ether, followed by drying under reduced pressure to give 18.9 g (yield: quantitative) of the title compound.

m.p.: 256-258 °C

IR: ν = 1650, 1625, 1560, 1490, 855, 750 cm^{-1}

Example 18

Synthesis of sodium salts of various carboxylic acids having thiazole groups

By carrying out the treatment similarly as in Example 17, the title compounds shown as compounds Nos. 214-395 and 434-436 in Table 2 were obtained.

Example 19

Synthesis of 2-[trans-3-(3-carboxypropyl)aminostyryl]benzothiazole sodium salt (compound No. 396)

To 8 ml of ethanol were added 1.16 g of 2-[trans-3-(3-ethoxycarbonylpropyl)aminostyryl]benzothiazole and 5 ml of 5% aqueous sodium hydroxide solution, and the mixture was stirred at 60 °C for 1.5 hours.

After evaporation of the solvent together with toluene under reduced pressure, the residue was diluted with ethanol and heated to 50 °C. After cooled to room temperature, the crystals formed were collected by filtration and washed with ethanol-ethyl ether, followed by drying under reduced pressure to give 1.11 g (yield 97%) of the title compound.

m.p.: 239-240 °C

IR: ν = 1360, 1570, 1410, 940, 760 cm^{-1}

Example 20

Synthesis of sodium salts of various carboxylic acids having thiazole groups

By carrying out the treatment similarly as in Example 19, the title compound shown as compounds Nos. 397-413 in Table 2 were obtained.

Example 21

Synthesis of 2-[trans-3-(cis-2-carboxycyclohexanoyl)aminostyryl]benzothiazole N-methyl-D-glucamine salt - (compound No. 414)

Into a solvent mixture of 6 ml of methanol and 1 ml of water were added 96 mg of N-methyl-D-glucamine and 200 mg of 2-[trans-3-(cis-2-carboxycyclohexanoyl)aminostyryl]benzothiazole and the mixture was stirred at room temperature for 30 minutes. After evaporation of the solvent under reduced pressure, the crude crystals formed were recrystallized from ethanol-ethyl ether to obtain 215 mg (yield 73%) of the title compound.

m.p.: 113-115 °C, 245-246 °C

IR: ν = 1680, 1540, 1410, 1080, 750 cm^{-1}

Example 22

Synthesis of salts with organic bases of various carboxylic acids having thiazole groups

By carrying out the treatment similarly as in Example 21, the title compounds shown as compounds Nos. 415-421 in Table 2 were obtained. In Table 2, the following abbreviations were used.

NMG: N-methyl-D-glucamine,

Tris: tris(hydroxymethyl)aminomethane

Example 23

Synthesis of 2-[trans-3-(4-hydroxybutanoylamino) styryl]benzothiazole (compound No. 422)

A solution of 1.0 g of 2-(trans-3-aminostyryl)-benzothiazole dissolved in 15 ml of anhydrous tetrahydrofuran was cooled to -78 °C and 2.8 ml of a n-hexane solution (1.55M) of n-butyl lithium was added dropwise in a nitrogen gas atmosphere. After a mixture was stirred at the same temperature for 25 minutes, 375 mg of γ-butyrolactone was injected, followed by stirring for 1 hour. After completion of the reaction, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crude crystals obtained were washed with ethyl ether and dried to obtain 160 mg (yield 12%) of the title compound.

m.p.: 191-192 °C

IR: ν = 3400, 1640, 1580, 1530, 1420, 1050, 940, 755 cm^{-1}

Example 24

Synthesis of 2-[trans-3-(4-hydroxybutoxy)styryl]benzothiazole (compound No. 423)

To 40 ml of ethyl ether was added 1.0 g of 2-[trans-3-(3-ethoxycarbonylpropoxy)styryl]benzothiazole, and 114 mg of lithium aluminum hydride was added under ice-cooling. After the mixture was stirred at the same temperature for 30 minutes, then at room temperature for 40 minutes, 114 μl of water, 114 μl of 15% aqueous sodium hydroxide and 340 μl of water were successively added slowly to decompose the

aluminum complex, followed by extraction with toluene. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure and the crude crystals formed were washed with ethyl ether under ice-cooling, followed by drying under reduced pressure to give 570 mg (yield 64%) of the title compound.

m.p.: 88-90 °C

IR: ν = 3280, 1590, 1570, 1285, 950, 760 cm^{-1}

Example 25

Synthesis of 2-[trans-3-(3-(5-tetrazolyl)propylamino)styryl]benzothiazole (compound No. 424)

To 5 ml of dimethylformamide were added 390 mg of sodium azide and 638 mg of 2-[trans-3-(3-cyanopropylamino)styryl]benzothiazole, and the mixture was heated to 120 °C for 7 hours. After cooled to room temperature, the mixture was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and the solvent was evaporation under reduced pressure. The concentrate was purified through silica gel column chromatography by use of ethyl acetate to obtain 250 mg (yield 35%) of the title compound.

m.p.: 168-169 °C

IR: ν = 1625, 1595, 1460, 1430, 950, 760 cm^{-1}

Example 26

Synthesis of 2-[trans-3-(2-carboxyanilino)styryl] benzothiazole (compound No. 425)

To 10 ml of isoamyl alcohol were added 504 mg of 2-(trans-3-aminostyryl)benzothiazole, 311 mg of 2-chlorobenzoic acid, 290 mg of potassium carbonate, 1 mg of iodine and 15 mg of copper powder, and the mixture was refluxed for 6 hours. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate. The crude product after evaporation of the solvent was purified through silica gel column chromatography by use of ethyl acetate-toluene to obtain 83 mg (yield 11%) of the title compound.

IR: ν = 1630, 1570, 1380, 1285, 1200, 750 cm^{-1}

m.p.: 146-150 °C

Example 27

Synthesis of 2-[trans-3-(2-carboxyethylamino) styryl]benzothiazole sodium salt (compound No. 426)

To 1 ml of acetonitrile were added 1.0 g of 2-(trans-3-aminostyryl)benzothiazole and 1 ml of β-propiolactone, and the mixture was refluxed for 1 hour. After evaporation of acetonitrile under reduced pressure, toluene and 10% hydrochloric acid were added to the residue. After the insolubles were filtered off, the filtrate was made alkaline with addition of 10% aqueous sodium hydroxide solution and the precipitates formed were collected by filtration. The crude product was recrystallized from methanol-ethyl acetate to obtain 224 mg (yield 16%) of the title compound.

m.p.: 250 °C (decomposed)

IR: ν = 1565, 1405, 1005, 940, 750 cm^{-1}

Example 28

Synthesis of 2-[3-(2-carboxyethylamino)styryl]-4,5-dimethylthiazole sodium salt (compound No. 427)

An amount of 230 mg of 2-(trans-3-aminostyryl)-4,5-dimethylthiazole, 1 ml of methyl acrylate and two drops of acetic acid were added to 1.5 ml of toluene and the mixture was refluxed for 16 hours. The mixture was extracted in a conventional manner with ethyl acetate, the solvent was evaporated under reduced pressure and the residue was purified through silica gel column chromatography by use of ethyl acetate-n-hexane to obtain 160 mg of acrylate adduct. Next, 160 mg of the ester was dissolved in 5 ml of ethanol, and 2 ml of 5% aqueous sodium hydroxide was added to carry out hydrolysis by stirring at room temperature for 1 hour. The precipitates formed were collected by filtration, washed with water and then with ethyl ether, followed by drying under reduced pressure to obtain 90 mg (yield 28%) of the title compound.

m.p.: 120-123 °C

IR: ν = 1595, 1550, 1405, 945, 765 cm^{-1}

Example 29

Synthesis of 2-[trans-3-(2-carboxyethylamino) styryl]-4-phenylthiazole sodium salt (compound No. 428)

By carrying out the treatment similarly as in Example 28, 93 mg (yield 23%) of the title compound was obtained.

m.p.: 261-263 °C (decomposed)

IR: ν = 1700, 1590, 1440, 1220, 1195, 760 cm^{-1}

Example 30

Synthesis of 2-[trans-3-(2-carboxyethoxy)styryl] benzothiazole (compound No. 429)

To 3 ml of dimethylformamide were added 47 mg of 60% sodium hydride and 300 mg of 2-(trans-3-hydroxystyryl)benzothiazole, and the mixture was stirred at room temperature for 30 minutes. Then, 74 µl of β-propiolactone was added and the mixture was further stirred for 4.5 hours. The acidic portion was extracted in a conventional manner with chloroform, and after drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure and the crude crystals were washed with ethyl ether, followed by drying under reduced pressure to give 118 mg (yield 31%) of the title compound.

m.p.: 177-178 °C

IR: ν = 1705, 1590, 1440, 1215, 1195, 960, 760 cm^{-1}

Example 31

Synthesis of 2-[trans-3-(3-carboxy-3,3-dimethylpropyloxy)styryl]-4-isopropylthiazole (compound No. 430)

To a solution of 200 mg of 2-[trans-3-(3,3-dimethyl-3-ethoxycarbonylpropyloxy)styryl]-4-isopropylthiazole dissolved in 5 ml of ethanol were added 2 ml of 10% aqueous potassium hydroxide solution and three drops of 40% benzyltrimethylammonium hydroxide methanol solution, and the mixture was refluxed for 1 hour to effect hydrolysis of the ester. After completion of the reaction, ethanol was evaporated under reduced pressure and the residue was adjusted to pH 1-2 with addition of 10% hydrochloric acid and then extracted with ethyl ether. After drying of anhydrous magnesium sulfate, the solvent was evaporated and the solid formed was recrystallized from methanol to give 123 mg (yield 66%) of the title compound.

m.p.: 112-113 °C

IR: ν = 1705, 1285, 1160, 1100, 740 cm^{-1}

Example 32

Synthesis of various styrylcarboxylic acids

By carrying out the treatment similarly as in Example 31, the title compounds shown as compounds Nos. 438-444 in Table 2 were obtained.

Example 33

Preparation of tablets

An amount of 1000 g of well pulverized 2-[trans-3-(cis-3-carboxypropenamide)styryl]benzothiazole sodium salt (compound No. 213), 5900 g of lactose, 2000 g crystalline cellulose, 1000 g of a low substitution degree hydroxypropyl cellulose and 100 g of magnesium stearate were well mixed and formed into plain tables according to the direct tableting method containing 10 mg of the above compound in 100 mg of one tablet. The plain tablet was applied with sugar coating or film coating to prepare sugar-coated tablet and film-coated tablet.

Example 34

Preparation of capsules

An amount of 1000 g of well pulverized 2-[trans-3-(cis-3-carboxypropenamide)styryl]benzothiazole sodium salt (compound No. 213), 3000 g of corn starch, 6900 g of lactose, 1000 g of crystalline cellulose and 100 g of magnesium stearate were mixed to prepare capsules containing 10 mg of the above compound in 120 mg of one capsule.

Example 35

Preparation of inhalent

An amount of 5 g of well pulverized 2-[trans-3-(cis-3-carboxypropenamide)styryl]benzothiazole sodium salt (compound No. 213), 10 g of a middle chain saturated fatty acid triglyceride and 0.2 g of sorbitane monooleate were well mixed, and each 15.2 mg of the mixture was weighed in 5 ml of an aluminum vessel for aerosol. Further, after 84.8 mg of Freon 12/114 (1 : 1 mixture) was filled per one vessel at low temperature, the vessel was equipped with a quantitative adaptor of 100 ul per 1 spray to prepare an inhalent of quantitative spray containing 5 mg of the above compound in 5 ml of one vessel.

Example 36

SRS antagonistic action in vitro

The ileum end portion of a male Hartley-strain guinea pig weighing 200-450 g was extirpated and after washing its lumen, the ileum was mounted within 5 ml of a tissue bath containing a Tylord solution comprising the following components. The components are 136 mM NaCl, 2.7 mM KCl, 11.9 mM $NaHCO_3$, 1.05 mM $MgCl_2$, 1.8 mM $CaCl_2$, 0.4 mM NaH_2PO_4 and 5.6 mM glucose. The liquid temperature in the bath was maintained at 37 °C, and aeration was effected with 95% oxygen / 5% carbon dioxide. For removing shrinkage with hystamine and acetylcholine, 10^{-7} g/ml of mepylamin and 5×10^{-8} g/ml of atropin were added to the above buffer. Isotonic measurement was conducted by isotonic transducer (TD-112S, trade name, produced by Nippon Koden) tension replacement convertor and recorded by Recticoder (RTG-4124, trade name, produced by Nippon Koden) as the change in grams of tension. The ileum was loaded passively with 0.5 g of tension and the ileum shrinkage reaction to SRS extracted from guinea pig lung was obtained. The persistent shrinkage height by one unit of of SRS (corresponding to 5 ng of hystamine) was used as control. Test drugs of various concentrations were added into the tissue bath, and the results of minimum effective concentration which is the concentration of the test drug attenuating shrinkage of control to 50% (IC_{50}) are shown in Table 2 and Table 3.

Example 37

LTD_4 antagonistic action in vivo

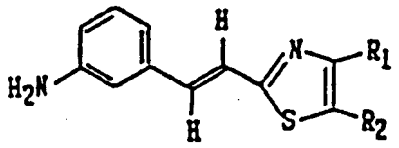
For male Hartley-strain guinea pig weighing 350-500 g under urethane anesthesia, airway resistance was measured by use of a Harvard type respirator according to the method which is a modification of the Konzett-Roessler method, inhibition (%) by intraduodenal administration of the test drug against airway resistance increase by intraveneous administration of 0.1-1.0 μg/kg of LTD_4 was calculated to obtain the results shown in Table 2 and Table 4.

Test example

Acute toxicity test

With 4 to 5 ddy-strain male mice of 6 weeks old as one group, the compound of the present invention was orally administered as a suspension in 1% tragacanth solution, and observation was conducted for 7 days and the number of dead mice was examined to obtain the results shown in Table 5.

Table 1-1

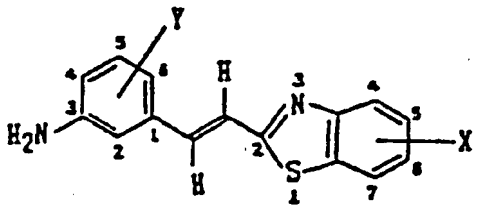


(IIa)

No.	R_1	R_2	m.p. (℃)
1	Me	Me	148～149
2	Et	〃	76～ 77
3	〃	H	60～ 61
4	$CH_3(CH_2)_2$-	〃	61～ 62
5	$CH_3(CH_2)_3$-	〃	79～ 80
6	$CH_3(CH_2)_4$-	〃	56～ 57
7	$CH_3(CH_2)_5$-	〃	65～ 66
8	$CH_3(CH_2)_6$-	〃	56～ 57
9	$CH_3(CH_2)_7$-	〃	50～ 51
10	$CH_3(CH_2)_2$-	Et	58～ 59
11	$(CH_3)_3C$-	H	74～ 75
12	Me	$CH_3(CH_2)_3$-	58～ 59
13	C_6H_5-	〃	138～139

No.	R_1	R_2	m.p. (℃)
14	-COOEt	H	83～ 84
15	$-(CH_2)_4-$		156～157
16	C_6H_5-	H	137～139
17	p-Cℓ $-C_6H_4-$	〃	177～178
18	m-Me-C_6H_4-	〃	117～118
19	p-EtOOC-C_6H_4-	〃	145～146
20	p-Me-C_6H_4-	〃	156～157
21	p-MeO-C_6H_4-	〃	141～142

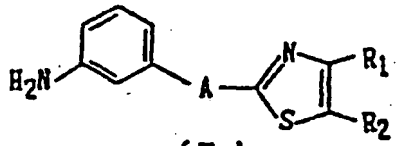
Table 1-2



(IIb)

No.	X	Y	m.p. (℃)
22	H	H	178～179
23	5-OMe	〃	143～144
24	5-Me	〃	150～151
25	5-Cℓ	〃	168～169
26	6-OMe	〃	158～160
27	H	2-Me	118～120
28	〃	6-OMe	147～148
29	〃	4-Cℓ	174～176
30	〃	6-Cℓ	191～192
31	〃	2-OH	180～181
32	〃	4-OMe	155～156
33	〃	6-OH	234～236

Table 1-3



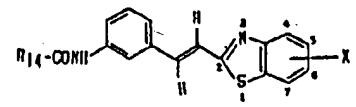
(IIc)

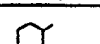
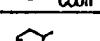
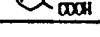
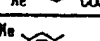
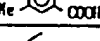
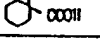
No.	R_1	R_2	A	m.p. (℃)
34			$-(CH_2)_2-$	79～ 80
35	$(CH_3)_2CH-$	H	〃	－*
36	H	〃	$-CH_2OCH_2-$	－**
37	〃	〃	$-OCH_2-$	120～121
38	〃	〃	$-NHCH_2-$	102～103

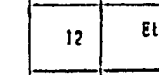
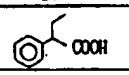
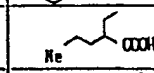
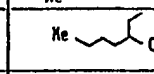
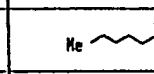
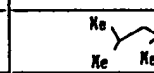
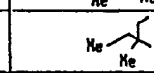
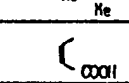
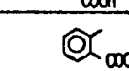
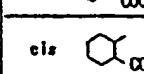
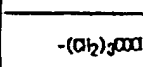
* IR: 1600、1450、1160、1100、 770、 730

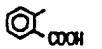
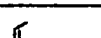
** IR: 1620、1460、1310、1090、 865、 760

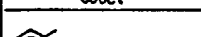
Table 2-1

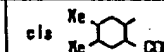
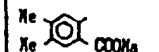
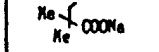
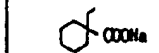
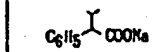
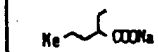
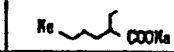
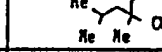
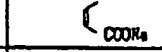
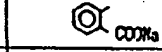
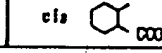


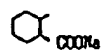
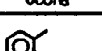
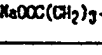
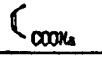
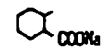
Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
2		II	193~ 4	IR 1700, 1670, 1580, 1541, 1200, 750	5×10^{-9}	
3	cis 	〃	191~ 2	IR 1705, 1660, 1542, 1488, 1080, 755	5×10^{-9}	
4	cis 	〃	190~ 3	IR 1705, 1660, 1600, 1540, 950, 760		
5	trans 	〃	230~ 7	IR 1715, 1650, 1530, 1080, 950, 750		
6	$-(CH_2)_2COOH$	〃	219~ 20	IR 1690, 1540, 1315, 1210, 760		
7	$-(CH_2)_3COOH$	〃	227~ 30	IR 1705, 1640, 1530, 1415, 1080, 765		
8	cis 	〃	189~ 90	IR 1690, 1670, 1410, 1200, 950, 750		
9		〃	108~202	IR 1705, 1650, 1540, 1250, 780		
10		〃	108~171	IR 1660, 1550, 1495, 1440, 1215, 955, 755		
11		〃	177~ 8	IR 1710, 1670, 1545, 1200, 755		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
12		H	160~ 1	IR 1690, 1540, 1200, 950, 750		
13		〃	191~ 2	IR 1705, 1660, 1540, 1180, 755		
14		〃	169~ 70	IR 1700, 1660, 1540, 1200, 950, 750		
15		〃	163~ 4	IR 1710, 1680, 1540, 750		
16		〃	140~ 1	IR 1700, 1655, 1540, 1310, 950, 750		
17		〃	191~ 2	IR 1680, 1540, 1417, 1190, 753		
18		〃	169~ 70	IR 3210, 2950, 1680, 1540, 1000, 950, 750		
19		5-Me	211~ 2	IR 1695, 1620, 1550, 1400, 850, 705		
20		〃	207~ 8	IR 1705, 1650, 1260, 940, 700, 690		
21	cis 	〃	184~ 5	IR 1715, 1660, 1525, 1200, 945, 700		
22	$-(CH_2)_2COOH$	〃	249~ 50	IR 1710, 1650, 1580, 1180, 945, 800		
23	$-(CH_2)_3COOH$	〃	236~ 8	IR 1710, 1655, 1425, 1200, 855, 700		
24		5-Cl	224~ 5	IR 1695, 1550, 1400, 950, 855, 785		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
25		5-Cl	249~ 50	IR 1700, 1580, 1230, 1065, 705		
26	cis 	〃	189~ 90	IR 1700, 1520, 1350, 1200, 950, 800		
27	$-(CH_2)_2COOH$	〃	244~ 5	IR 1690, 1650, 1580, 1200, 940, 800		
28	$-(CH_2)_3COOH$	〃	226~ 7	IR 1705, 1660, 1540, 1200, 945, 800		
29		5-OMe	199~200	IR 1730, 1690, 1550, 1180, 850, 700		
30		〃	198~ 9	IR 1710, 1580, 1235, 950, 780		
31	cis 	〃	>350	IR 1700, 1550, 1405, 1180, 1120, 850, 790		
32	$-(CH_2)_2COOH$	〃	251~ 2	IR 1700, 1650, 1180, 940, 800		
33	cis 	8-OMe	208~ 8	IR 1710, 1600, 1500, 1540, 1485, 1260, 1180, 830		
167		II	277~ 80	NMR ($CDCl_3$-DMSO-d_6) : δ = 6.56(2H,d), 6.83~6.8(11H, m), 10.07(1H, s)	2×10^{-7}	
168	HOOC-	〃	213~ 5	NMR ($CDCl_3$-DMSO-d_6): δ = 7.33~8.30(11H, m), 10.73(1H, broad s)	10^{-7}	
184		〃	180~ 1.5	IR 1705, 1680, 1545, 1300, 760		
185	EtOOC-	〃	150~ 4	IR 1730, 1700, 1300, 1200, 770		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
186	$EtOOCCH_2-$	H	134~ 7	IR 1740, 1650, 1580, 1440, 1150, 840, 750		
190		〃	130~ 1	IR 1605, 1515, 1580, 1210, 750		
191		〃	132~ 3	NMR ($CDCl_3$): δ = 1.02(6H,d), 1.27~1.00(3H,m), 4.18(2H,m), 6.82~8.25(8H,m)		
192	$MeOOC(CH_2)_2-$	〃	140~ 1	IR 1735, 1680, 1580, 1550, 1420, 1155, 950, 760	5×10^{-7}	
193	$EtOOC(CH_2)_2-$	〃	148~ 50	IR 1720, 1680, 1540, 1175, 765		
194		〃	149~ 51	IR 1730, 1690, 1178, 853, 750		
195		〃	82~ 3	IR 1720, 1580, 1440, 1200, 755		
214		〃	171~ 3	IR 1560, 1490, 1445, 1220, 850		
215		〃	274~ 7	IR 1640, 1600, 1580, 1560, 1380, 743		
216	cis	〃	255~ 7	IR 1640, 1550, 1493, 1405, 750		65
217	cis 	〃	150~ 60	IR 1680, 1580, 1420, 1305, 750		
218	$NaOOC(CH_2)_2-$	〃	248~ 50	IR 1665, 1580, 1415, 945, 735		
219	$NaOOC(CH_2)_3-$	〃	260~ 2	IR 1650, 1550, 1410, 940, 750		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
220	cis 	〃	180~ 3	IR 1705, 1560, 1405, 1310, 700		
221		〃	197~202	IR 1625, 1580, 1400, 950, 700		
222		〃	150~ 5	IR 1055, 1540, 945, 870, 750		
223		〃	168~ 71	IR 1600, 1550, 1405, 1440, 1215, 955, 755		
224		〃	120~ 5	IR 1650, 1540, 1210, 940, 750		89
225		〃	125~ 30	IR 1635, 1540, 1305, 925, 730		
226		〃	125~ 30	IR 1650, 1545, 1400, 950, 750		
227		〃	180~ 3	IR 1605, 1550, 950, 750	5×10^{-9}	
228		〃	200~ 1	IR 2910, 1655, 1545, 1305, 750		
229		〃	145~ 50	IR 1650, 1540, 1210, 950, 750		
230		5-Me	225~ 8	IR 1680, 1590, 1440, 1305, 950, 700		
231		〃	273~ 5	IR 1600, 1580, 1550, 945	5×10^{-9}	
232	cis 	〃	200~303	IR 1680, 1580, 1530, 1400, 1300, 950, 785		89

Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibiton (%)
233	$NaOOC(CH_2)_2$-	〃	228~ 31	IR 1660, 1585, 1410, 950, 790		
234	$NaOOC(CH_2)_3$-	5-Me	213~ 5	IR 1655, 1570, 1535, 1410, 1200		
235	cis 	5-COOMe	330~ 5	IR 1700, 1585, 1540, 1400, 1300, 760		
236		5-Cl	257~ 60	IR 1630, 1580, 1480, 1430, 955		
237		〃	293~ 0	IR 1600, 1590, 1565, 1490, 1390		
238	cis 	〃	284~ 94	IR 1680, 1580, 1530, 1400, 950, 790		
239	$NaOOC(CH_2)_2$-	〃	230~ 4	IR 1655, 1580, 1540, 1430, 940		
240	$NaOOC(CH_2)_3$-	〃	215~ 7	IR 1650, 1570, 1540, 1430, 940		
241		5-OMe	215~ 7	IR 1630, 1585, 1430, 1280, 950, 800		
242		〃	295~ 8	IR 1675, 1590, 1540, 1490, 1390		
243	cis 	〃	>350	IR 1660, 1600, 1270, 1190, 800		
244	$NaOOC(CH_2)_2$-	〃	241~ 3	IR 1655, 1550, 1420, 950, 725		
245	cis 	8-OMe	260~ 5	IR 1680, 1585, 1400, 1280, 950, 800		

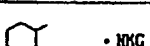
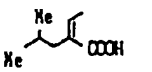
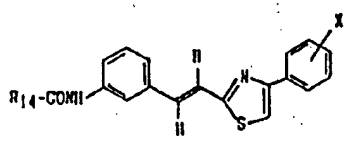
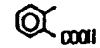
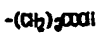
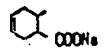
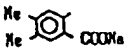
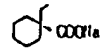
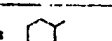
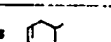
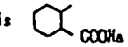
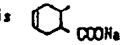
Compound No.	R_{14}	X	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
415	 · Tris	II	179~ 80	IR 1625, 1560, 1350, 1330, 1060, 750		
416	· Tris	〃	108~ 9	IR 1625, 1615, 1550, 1380, 1050, 750		
417	 · MNG	〃	135~ 40 224~ 5	IR 1650, 1550, 1475, 1080, 755		
418	Trans  · MNG	〃	95~ 6 (decomposition)	IR 1660, 1550, 1400, 1080, 750		
419	$HOOC(CH_2)_2$- · Tris	〃	102~ 3	IR 1630, 1605, 1600, 1580, 1410, 1060, 750		
445		〃	133~ 5	IR 1695, 1630, 1520, 1190, 750		

Table 2-2



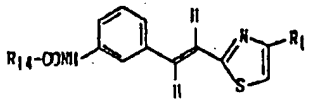
Compound No.	R_{14}	X	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
34		H	199~200	1740, 1720, 1700, 1620, 1540, 1400, 845, 725	2×10^{-8}	
35		〃	201~ 5	1720, 1620, 1575, 1550, 1242, 735		
36	cis 	〃	205~ 8	1695, 1680, 1540, 1440, 1280, 845, 750		
37	cis 	〃	204~ 5	1690, 1540, 1410, 1200, 940, 755		
38	$-(CH_2)_2COOH$	〃	237~ 8	1680, 1650, 1530, 1405, 735		
39	$-(CH_2)_3COOH$	〃	190~ 2	1700, 1650, 1595, 1400, 950, 725		
40	cis 	〃	158~ 60	3300, 2950, 1700, 1545, 1190, 950, 725		
41	cis 	〃	202~ 3	1700, 1542, 1185, 945, 755		
42		〃	184~ 5	1685, 1680, 1600, 1320, 950, 730		
43		〃	182~ 4	1660, 1550, 1400, 1440, 1210, 955, 755		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
44		p-Cl	204~ 7	1695, 1615, 1530, 1395, 1080, 945, 840, 735		
45		〃	218~ 20	1720, 1640, 1620, 1610, 1580, 1245, 780, 700		
46	cis 	〃	214~ 5	1680, 1580, 1470, 1400, 940, 825, 770		
47	cis 	〃	210~ 3	1685, 1590, 1540, 1200, 940, 770		
48	$-(CH_2)_3COOH$	〃	179 ~ 81	1685, 1655, 1595, 1530, 1400, 950, 740		
49	cis 	p-Me	203~ 4	1692, 1540, 1180, 950, 775		
50	cis 	〃	202~ 3	1690, 1540, 1200, 945, 775		
51	cis 	m-Me	197~ 8	1690, 1540, 1180, 940, 770		
52	cis 	p-OMe	187~ 9	1685, 1530, 1260, 1175, 770		
53	cis 	p-COOEt	204~ 5	1705, 1545, 1415, 1280		
246		II	225~ 9	1650, 1580, 1440, 950, 735		
247		〃	268~ 70	1660, 1580, 1550, 1480, 1380, 850, 730		
248	cis 	〃	234~ 5	1642, 1540, 1400, 955, 735		85

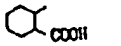
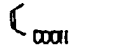
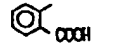
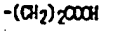
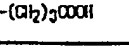
Compound No.	R_{14}	X	m.p. (℃)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
248	cis 	H	149~ 50	1650, 1540, 1400, 955, 720		
250	$NaOOC(CH_2)_2$-	〃	205~ 8	1645, 1555, 1430, 1410, 815, 735		
251	$NaOOC(CH_2)_3$-	〃	275~ 7	1680, 1600, 1540, 1400, 955, 730		
252	cis 	〃	170~ 4 (decomposition)	1665, 1550, 1405, 950, 730		
253		〃	150~ 2 (decomposition)	1650, 1580, 1400, 1400, 950	5×10^{-6}	
254		〃	130~ 9	1660, 1550, 1490, 1440, 1210, 955, 755		
255		p-Cl	225~ 8	1580, 1470, 1085, 945, 735		
256		〃	307~ 20	1680, 1610, 1590, 1530, 1385, 705		
257	cis 	〃	273~ 5	1660, 1550, 1465, 1080, 845, 825, 740		
258	cis 	〃	150~ 62	1660, 1560, 1470, 1400, 1085, 710		
259	$NaOOC(CH_2)_3$-	〃	208~ 01	1660, 1600, 1550, 1400, 1095, 955, 745		
260	cis 	p-Me	255~ 8	1665, 1580, 1480, 1405, 950, 740		
261	cis 	〃	152~ 3	1680, 1550, 1480, 1405, 950, 740		

Compound No.	R_{14}	X	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
262	cis	m-Me	170~ 80	1660, 1540, 1400, 950, 780, 730		
263	"	p-CMe	>200	1605, 1590, 1480, 1240, 745		
264	"	p-COOMe	>340	1690, 1590, 1540, 1400, 1290, 740		

Table 2-3

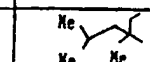
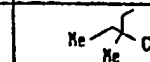
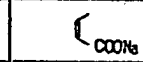
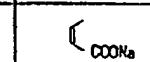


Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc: (M)]	Airway resistance increase inhibition (%)
54		Me	157~ 8	1700, 1620, 1550, 965, 855	5×10^{-7}	
55	$-(CH_2)_2COOH$	〃	199~200	1720, 1640, 1530, 1080, 945		
56	$-(CH_2)_3COOH$	〃	208~ 10	1705, 1645, 1525, 1080, 950		
57		Et	149~ 50	1690, 1620, 1530, 950		
58		〃	181~ 3	1720, 1580, 1550, 1245, 700		
59	cis 	〃	132~ 3	1690, 1655, 1540, 1200, 790		
60	$-(CH_2)_2COOH$	〃	191~ 2	1690, 1540, 1320, 1190, 780		
61	$-(CH_2)_3COOH$	〃	146~ 7	1705, 1643, 1530, 1180, 950, 780		
62		$CH_3(CH_2)_2-$	151~ 2	1700, 1620, 1550, 1410, 000		
63		〃	100~ 1	1720, 1625, 1580, 1245, 781		

Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
64	cis 	$CH_3(CH_2)_2$-	171~ 2	1685, 1540, 1200, 785		
65	-$(CH_2)_2$COOH	〃	173~ 4	1605, 1540, 1320, 1180, 950, 775		
66	-$(CH_2)_3$COOH	〃	130~ 1	1715, 1640, 1440, 1185, 950, 775		
67		$CH_3(CH_2)_3$-	151~ 3	1695, 1615, 1545, 1400, 950, 835		
68		〃	168~ 8	1715, 1650, 1575, 1480, 1240, 950, 780		
69	-$(CH_2)_2$COOH	〃	149~ 51	1700, 1680, 1540, 1480, 1320, 950, 755		
70	-$(CH_2)_3$COOH	〃	81~ 3	1600, 1650, 1600, 1555, 1405, 1135, 950, 775		
71		$CH_3(CH_2)_4$-	143~ 4	1700, 1550, 1410, 970, 800		
72		〃	178~ 9	1720, 1620, 1575, 1550, 1415, 1240, 960, 775		
73	cis 	〃	161~ 3	1600, 1540, 1440, 1410, 1200, 945		
74	cis 	〃	153~ 5	1690, 1540, 1410, 1200, 945		
75	-$(CH_2)_2$COOH	〃	149~ 51	1710, 1650, 1580, 1440, 1180, 945		
76	-$(CH_2)_3$COOH	〃	87~ 8	1680, 1650, 1605, 1540, 1200, 780		

Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values(IR)	Anti-SRS action (minimum effective conc. (M))	Airway resistance increase inhibition (%)
77		$CH_3(CH_2)_5$-	142~ 3	1700, 1620, 1555, 1535, 1405, 865		
78		〃	175~ 8	1710, 1625, 1580, 1550, 1250		
79	-$(CH_2)_2$-	〃	145~ 8	1720, 1600, 1585, 1530, 1440		
80	-$(CH_2)_3$	〃	140~ 1	1715, 1645, 1580, 1530		
81		$CH_3(CH_2)_6$-	140~ 1	1700, 1555, 1407, 860		
82		〃	155~ 7	1720, 1622, 1580, 1243, 905, 700		
83	-$(CH_2)_2$	〃	144~ 5	1720, 1660, 1530, 1180, 960, 700		
84	-$(CH_2)_3$	〃	127~ 8	1710, 1653, 1530, 785		
85	cis	$CH_3(CH_2)_7$-	160~ 2	1685, 1540, 1200, 840		
86		$(CH_3)_2CF$-	105~ 6	1700, 1550, 1405, 960, 880		
87		〃	167~ 8	1720, 1580, 1230, 955, 700		
88	-$(CH_2)_2$	〃	171~ 2	1720, 1660, 1165, 960, 730		
89	-$(CH_2)_3$	〃	138~ 40	1705, 1680, 1550, 1220, 900, 730		

Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
90		$(CH_3)_2CH-$	148~ 9	1695, 1615, 1540, 1300, 845		
91		〃	118~ 20	1690, 1620, 1525, 950		
92		〃	182~ 3	1720, 1580, 1240, 853, 778		
93	cis 	〃	169~ 70	1705, 1640, 1533, 1185, 955		
94	$-(CH_2)_2COOH$	〃	150~ 0	1700, 1680, 1580, 1410, 955, 790, 740		
95	$-(CH_2)_3COOH$	〃	143~ 4	3270, 1710, 1640, 1440, 1180, 940		
96		〃	175~ 8	1690, 1550, 1450, 960, 705		
97		〃	175~ 8	2950, 1710, 1650, 1180, 950, 775		
98		〃	180~ 1	1707, 1640, 1543, 1170, 960, 703		
99		〃	199~200	1705, 1660, 1540, 960, 855		
100		〃	155~ 8	1705, 1655, 1540, 1170, 955, 780		
101		〃	147~ 8	1705, 1657, 1105, 955, 780		
102		〃	154~ 5	1680, 1540, 1405, 1190, 950, 705		

Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values(IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
103		〃	175～ 8	1680, 1540, 950, 780		
104		$(CH_3)_2CH$-	155～ 8	3300, 2950, 1600, 1540, 950, 700		
265		Me	150～ 7	1630, 1550, 1440, 940, 850, 765		
266	〃	Et	135～ 40	1600, 1555, 1440, 950, 850, 780		
267		〃	152～ 5	1650, 1560, 1385, 955, 780		
268	cis 	〃	144～ 8	1600, 1547, 1405, 950, 780		
269	$NaOOC(CH_2)_2$-	〃	185～ 70	1600, 1555, 1410, 950, 795		
270	$NaOOC(CH_2)_3$-	〃	210～ 1	1645, 1550, 1410, 950, 785		
271		$-(CH_2)_2CH_3$	118～ 20	1600, 1560, 1440, 950, 780		
272		〃	161～ 3	1640, 1585, 1580, 950, 780		
273	cis 	〃	137～ 40	1660, 1550, 1405, 950, 780		
274	$NaOOC(CH_2)_2$-	〃	103～ 5	1660, 1550, 1410, 1150, 950, 780	10^{-7}	
275	$NaOOC(CH_2)_3$	〃	195～ 7	1650, 1555, 1410, 950, 785		

Compound No.	R_{14}	R_1	m.p. (℃)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
276		$-(CH_2)_4CH_3$	123~ 7	1695, 1615, 1545, 1460, 950, 855		
277		$-(CH_2)_3CH_3$	120~ 5	1650, 1600, 1580, 1560, 1385, 1325, 955		
278	$NaOOC(CH_2)_2-$	〃	185~ 90	1605, 1560, 1410, 950, 705		
279	$NaOOC(CH_2)_3-$	〃	187~ 92	1650, 1580, 1555, 1435, 1410, 955		
280		$-(CH_2)_4CH_3$	135~ 8	1660, 1555, 1430, 948, 850		
281		〃	118~ 20 (decomposition)	1660, 1545, 1410, 955, 700		
282	cis	〃	135~ 40	1660, 1545, 1410, 950, 700		
283	cis	$-(CH_2)_4CH_3$	95~ 98	1660, 1560, 1410, 950, 700		
284	$NaOOC(CH_2)_2-$	〃	170~ 6	1660, 1555, 1410, 945, 700		
285	$NaOOC(CH_2)_3-$	〃	225~ 8	1648, 1545, 1410, 948, 787		
286		$-(CH_2)_4CH_3$	115~ 7	1605, 1570, 1440, 955, 850		
287		〃	118~ 20	1650, 1600, 1580, 1560, 1390, 955	2×10^{-8}	
288	$NaOOC(CH_2)_2-$	〃	178~ 80	1660, 1555, 1410, 950		

Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
289	$NaOOC(CH_2)_3-$	〃	107~ 70	1650, 1550, 1410, 955		
290		$-(CH_2)_6CH_3$	125~ 7	1660, 1560, 1440, 950, 850, 780		
291		〃	114~ 8	1650, 1580, 1390, 955, 780	10^{-7}	
292	$NaOOC(CH_2)_2-$	〃	150~ 5	1660, 1550, 1410, 950, 705		
293	$NaOOC(CH_2)_3-$	〃	199~200	1650, 1595, 1415, 959, 700		
294	cis 	$-(CH_2)_7CH_3$	171~ 3	1650, 1540, 1400, 950, 780		
295		$-C(CH_3)_3$	154~ 8	1600, 1560, 1440, 1350, 950, 780		
298		〃	168~ 71	1640, 1580, 1560, 1385, 955, 740		
297	$NaOOC(CH_2)_2-$	〃	174~ 7	1660, 1600, 1560, 1415, 955		
298	$NaOOC(CH_2)_3-$	〃	192~ 3	1600, 1605, 1560, 1415, 955	5×10^{-8}	
299		$-CH((CH_3)_2$	140~ 5	1660, 1560, 1440, 1350, 950, 780		
300		〃	145~ 50	1650, 1600, 1555, 1380, 950, 740		
301	cis 	〃	130~ 2	1660, 1540, 1400, 955, 780		

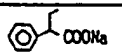
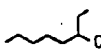
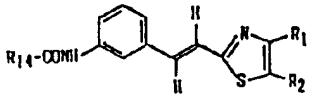
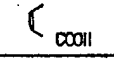
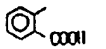
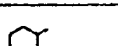
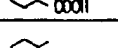
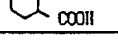
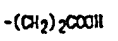
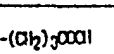
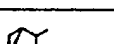
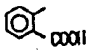
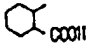
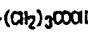
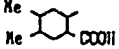
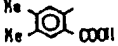
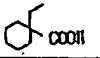
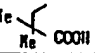
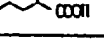
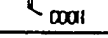
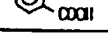
Compound No.	R_{14}	R_1	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
302	$NaOOC(CH_2)_2$-	〃	207~ 10	1660, 1550, 1410, 945, 780		
303	$NaOOC(CH_2)_3$-	$-CH(CH_3)_2$	260~ 70	1650, 1555, 1408, 943, 690		
304		〃	150~ 3	1660, 1550, 1445, 1400, 1210, 955, 780		
305		〃	120~ 6	1660, 1550, 1410, 850, 780		
306		〃	100~ 5	1650, 1540, 1400, 950, 780		
307		〃	127~ 30	1660, 1575, 1380, 930, 710	$2X10^{-9}$	
308		〃	120~ 5	1660, 1550, 1260, 960, 785		96
309		〃	55~ 60	1650, 1550, 1400, 950, 780		
310		〃	130~ 5	1650, 1540, 1400, 850, 775		93
311		〃	120~ 3	1650, 1540, 1400, 850, 780		
312		〃	80~ 85	1650, 1540, 1400, 850, 780		
446		$-(CH_2)_2CH_3$	159~ 60	1670, 1520, 1190, 960, 760		
447		〃	155~ 6	1670, 1540, 1410, 950, 780		
448		〃	164~ 5	1680, 1580, 1410, 1200, 955		

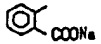
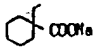
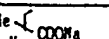
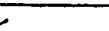
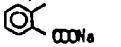
Table 2-4

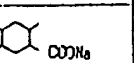
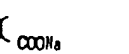
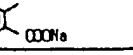
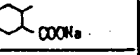
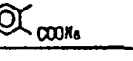
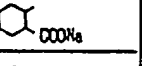
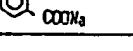


Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
105		Me, Me	150~ 2	1705, 1620, 1500, 1540, 940, 840		
106		〃	181~ 3	1700, 1650, 1545, 1255, 785		
107	cis 	〃	175~ 7	1660, 1600, 1545, 1210, 900, 780		
108	trans 	〃	195~200	1705, 1655, 1605, 1545, 1100, 900, 780		
109	cis 	〃	197~200	1680, 1500, 1540, 1430, 1215, 950, 780		
110	$-(CH_2)_2COOH$	〃	203~ 4	1710, 1660, 1600, 1550, 1400, 1230, 790		
111	$-(CH_2)_3COOH$	〃	186~ 9	1700, 1660, 1600, 1550, 1210, 945		
112	cis 	〃	206~ 7	1675, 1540, 1405, 1200, 940, 785		
113		〃	167~ 70	1650, 1540, 1440, 780		
114		〃	180~200	1680, 1540, 1200, 950, 780		

Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
115		Et, Me	173~ 4	1670, 1540, 1410, 1260, 955, 800		
116		〃	180~ 7	1720, 1500, 1250, 950, 780		
117	cis 	〃	180~ 7	3320, 2910, 1680, 1540, 1410, 945, 780		
118	$-(CH_2)_2COOH$	〃	215~ 6	1600, 1540, 1300, 950, 700		
119	$-(CH_2)_3COOH$	〃	163~ 4	3270, 1710, 1650, 1530, 1200, 780		
120	cis 	〃	178~ 9	1700, 1660, 1540, 1210, 700		
121		〃	200~ 1	1703, 1650, 1540, 1250, 700		
122		〃	211~ 2	1680, 1540, 1410, 850, 785		
123		〃	200~ 10	1677, 1540, 1200, 950, 785		
124		〃	104~ 5	1700, 1655, 1600, 1540, 1175, 960, 785		
125		$CH_3(CH_2)_2$-, Et	144~ 5	1720, 1600, 1550, 848, 845		
126		〃	142~ 3	1700, 1438, 1380, 1100, 710		
127	cis 	〃	181~ 3	1690, 1650, 1540, 1210, 950, 780		

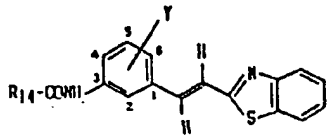
Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
128	$-(CH_2)_2COOH$	$CH_3(CH_2)_2-$, Et	160~ 1	1710, 1660, 1605, 1545, 950, 795		
129	$-(CH_2)_3COOH$	〃	81~ 2	1685, 1660, 1605, 1540, 1195, 780		
130		$C_6H_5-(CH_2)_3CH_2$	204~ 8	1720, 1620, 1580, 1545, 1295, 950, 780		
131	cis	〃	133~ 5	1690, 1580, 1530, 1410, 1200, 950, 785		
132		Me, $-(CH_2)_3CH_3$	173~ 8	1720, 1620, 1580, 1545, 1240, 955, 780		
133	cis	〃	104~ 7	1700, 1655, 1600, 1540, 1080, 960, 780		
134	cis	$-(CH_2)_2CH_3$, Et	181~ 3	1690, 1650, 1540, 1210, 950, 780		
135	cis	$-CONEt_2$, H	202~ 4	1690, 1545, 1415, 1205, 950, 730		
136		$-(CH_2)_4-$	190~ 3	1698, 1541, 1405, 850, 735		
137	$-(CH_2)_2COOH$	〃	230~ 7	1680, 1595, 1530, 1250, 804		
169		Me, Me	255~ 60	1710, 1670, 1600, 1545, 1250, 970, 785		
187		〃	163~ 4	1700, 1600, 1550, 1295, 1135, 780		
313		〃	163~ 7	1820, 1550, 1480, 1350, 1210, 940, 850		

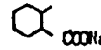
Compound No.	R_{14}	R_1, R_2	m.p. (℃)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
314		Me, Me	165~ 7	1655, 1580, 1550, 1385, 850, 780		
315	cis 	〃	177~ 9	1675, 1550, 1440, 1410, 850, 780		
316	Trans 	〃	242~ 8	1660, 1550, 1405, 845, 775		
317	cis 	〃	177~ 80	1660, 1575, 1540, 1430, 780		85
318	$NaOOC(CH_2)_2$-	〃	203~ 8	1650, 1630, 1580, 1410, 950, 780		
319	$NaOOC(CH_2)_3$-	〃	201~ 3	1655, 1555, 1410, 850, 780		
320		〃	167~ 70	1650, 1540, 1440, 1250, 950, 775		
321		〃	155~ 60	1660, 1540, 1400, 850, 780		
322		Et, Me	141~ 2	1660, 1555, 1435, 1350, 845, 780		
323		〃	151~ 3	1650, 1560, 1385, 850, 780		
324	cis 	〃	150~ 5	1665, 1545, 1405, 855, 780		
325	$NaOOC(CH_2)_2$-	〃	104~ 8	1660, 1560, 1410, 845		
326	$NaOOC(CH_2)_3$-	〃	205~ 10	1645, 1550, 1410, 950, 830, 780		

Compound No.	R_{16}	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
327	cis 	Et, Me	163~ 8 (decomposition)	1665, 1550, 1410, 955, 705		
328		〃	180~ 5	1650, 1550, 1405, 1320, 950, 700	5×10^{-9}	
329		〃	145~ 50	1655, 1545, 1440, 1210, 950, 780		
330		〃	145~ 50	1680, 1545, 1410, 1360, 950, 780		
331		〃	130~ 5	1650, 1540, 1400, 950, 780		
332		$Cl_3(CH_2)_2$-, Et	153~ 7	1660, 1560, 1440, 950, 850, 780	10^{-7}	
333		〃	195~ 7	1640, 1550, 1383, 950, 700		
334	cis 	〃	163~ 6	1655, 1540, 1405, 950, 700		
335	$NaOOC(CH_2)_2$-	〃	184~ 8	1660, 1550, 1405, 950, 775		
336	$NaOOC(CH_2)_3$-	〃	188~ 8	1650, 1550, 1405, 950, 780		
337		C_6H_5-, $-(CH_2)_3CH_3$	108~ 82	1580, 1550, 1480, 1385, 770, 690		
338	cis 	〃	153~ 5	1660, 1545, 1480, 1405, 770, 690		
339		Me, $-(CH_2)_3CH_3$	138~ 41	1645, 1545, 1380, 950, 780		

Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]	Airway resistance increase inhibition (%)
340	cis	Me,-$(CH_2)_9CH_2$	185~ 8	1660, 1540, 1410, 1405, 960, 780		
341	〃	-$(CH_2)_7CH_2$,Et	163~ 6	1655, 1540, 1405, 1300, 950, 780		
342	〃	-COOEt, H	177~ 80	1710, 1670, 1545, 1400, 1220, 780		
343		-$(CH_2)_4$-	210~ 50	1660, 1550, 1430, 1310, 810		
344	$NaOOC(CH_2)_2$-	〃	250~ 60	1665, 1585, 1520, 1400, 950, 810		

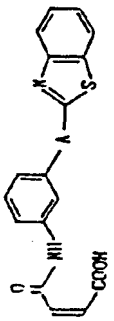
Table 2-5



Compound No.	R_{14}	Y	m.p. (°C)	Physcial property values (IR)
138	cis 	6-OH	304~ 6	1600, 1635, 1510, 1210, 960, 750
139	〃	4-Cl	176~ 8	1710, 1660, 1515, 1200, 945, 760
140	〃	2-Me	169~ 70 (decomposition)	1700, 1650, 1435, 1215, 955, 760
141	〃	4-OH	305~ 7	1600, 1640, 1500, 1445, 1260, 780
142	〃	4-OMe	179~ 80	1670, 1430, 1250, 1050, 760
143	〃	6-OMe	197~ 8 (decomposition)	1710, 1635, 1225, 1170, 960, 760
144	〃	2-OH	200 (decomposition)	3290, 2910, 1690, 1445, 750
145		〃	185~ 6	3300, 2950, 1680, 1630, 1445, 965, 750
345	cis 	6-OH	214~ 7	1610, 1540, 1400, 1240, 955, 750
346	〃	4-Cl	100~ 72	1650, 1560, 1400, 1040, 755

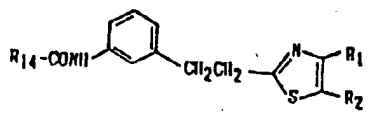
Compound No.	R_{14}	Y	m.p. (°C)	Physical property values (IR)
347	cis 	2-Me	188~201	1635, 1560, 1405, 850, 755
348	〃	4-OH	254~ 7	1680, 1590, 1510, 1200, 820, 760
349	〃	4-OMe	231~ 5	1670, 1565, 1530, 1255, 755
350	〃	6-OMe	178~ 82	1650, 1550, 1500, 1400, 1235, 1030, 760
351	〃	2-OH	240 (decomposition)	1680, 1540, 1190, 755
352	Et  Et	〃	200~ 5	1550, 1430, 960, 750

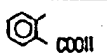
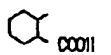
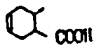
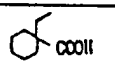
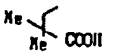
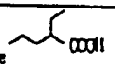
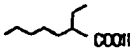
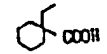
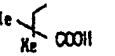
Table 2-6

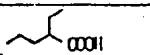
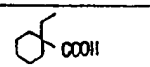
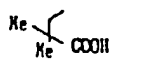
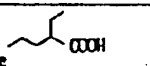
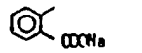
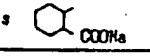
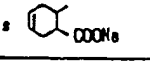
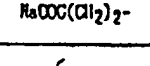
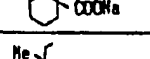
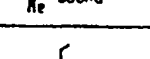


Compound No.	A	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]
146	$-OCH_2-$	182~ 3	1700, 1625, 1575, 1490, 755	
147	$-CH_2OCH_2-$	130~ 40	1700, 1625, 1555, 1530, 953, 753	
148	$-CONH-$	217~ 9	1670, 1540, 1290, 1200, 750	
149	$-CH=CH-CONH-$	240~ 1	1705, 1685, 1620, 1580, 1540, 1265, 1180, 750	
150	$-NHCH_2-$	158~ 9	1690, 1610, 1490, 840, 750	2×10^{-9}
151	$-(CH_2)_2-$	154~ 5	1700, 1620, 1550, 850, 760	

Table 2-7

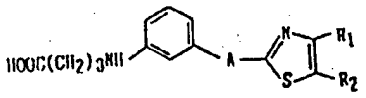


Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]
152			151~ 3	IR 1700, 1650, 1810, 1490, 1245	
153	cis 	〃	150~ 61	IR 1710, 1640, 1530, 1440, 1180, 750	
154	cis 	〃	–	IR 1710, 1605, 1550, 1200, 730 NMR(CDCl$_3$)2.15~2.75(6H,m), 2.75~3.55(4H,m),5.57(2H,d),8.75~8.10(8H,m)	
155	$-(CH_2)_2COOH$	〃	161~ 2	IR 1720, 1680, 1220, 1175, 760	
156		〃	158~ 9	IR 1687, 1650, 1540, 755	
157		〃	163~ 4	IR 1720, 1653, 1525, 1185, 755	
158		〃	130~ 1	IR 1710, 1600, 1540, 1180, 755	
159		〃	130~ 1	IR 2910, 1690, 1640, 1430	
160	cis 	$(CH_3)_2CH-$,H	125~ 6	IR 1670, 1600, 1535, 1440, 1210, 780	
161		〃	125~ 7	IR 1690, 1660, 1545, 1440, 1210, 730	

Compound No.	R_{14}	R_1, R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]
162		$(CH_3)_2CH-$, H	78~ 80	IR 1710, 1660, 1605, 1440, 1175, 780	
163		Et, Me	149~ 50	IR 2920, 1680, 1430, 1190, 785	
164		"	135~ 6	IR 1677, 1540, 1430, 1190, 705	
165		"	115~ 6	IR 1705, 1655, 1605, 1400, 1175, 700	
188	MeOOC-		112~ 3	NMR($CDCl_3$): δ=3.3~3.7(4H,m),3.98(3H,s),6.00~8.08(6H,m),8.80(1H,broad s)	
353		"	90~100 (decomposition)	IR 1560, 1435, 860,760	2×10^{-7}
354		"	116~ 20	IR 1650, 1500, 1560, 1385, 755	
355	cis 	"	223~ 7	IR 1680, 1560, 1405, 755	
356	cis 	"	201~ 10	IR 1680, 1550, 1425, 1200, 755	
357	$NaOOC(CH_2)_2$-	"	145~ 8	IR 1650, 1550, 1420, 750	
358		"	92~102	IR 1655, 1545, 1435, 755	10^{-8}
359		"	80~ 85	IR 2850, 1655, 1550, 1430, 955	
360		"	70~ 80	IR 2850, 1650, 1550, 1410, 950	

Compound No.	R_{14}	R_1 . R_2	m.p. (°C)	Physical property values	Anti-SRS action (minimum effective conc. (M))
361			55~ 60	IR 2910, 1645, 1545, 1400, 750	
362		-CH(CH$_3$)$_2$.H	86~ 88	IR 1650, 1540, 1440, 1205, 735	2×10^{-8}
363		〃	82~ 3	IR 1650, 1540, 1400, 1105, 735	
364		〃	87~ 70	IR 1650, 1540, 1400, 1180, 735	
365		Et . Me	95~100	IR 2010, 1650, 1545, 1300, 780	
366		〃	75~ 80 (decomposition)	IR 2950, 1650, 1540, 1435, 875, 780	5×10^{-8}
367		〃	120~ 1 (decomposition)	IR 2050, 1650, 1545, 1435, 1300, 780	

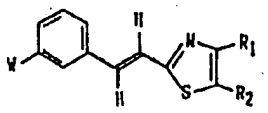
Table 2-8



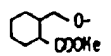
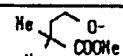
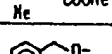
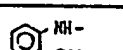
Compound No.	A	R_1, R_2	m.p. (°C)	Physical property values
171	-CH=CH-	$-(CH_2)_2CH_3$, Et	115~ 6	IR 1705, 1590, 1330, 1190, 940, 678
172	〃	$-CH(CH_3)_2$, H	112~ 3	IR 1690, 1590, 1405, 1105, 945, 775
173	〃	 , H	83~ 5	IR 1670, 1590, 1390, 945, 730
174	〃	Et, Me	129~ 30	IR 1705, 1600, 1330, 1190, 940, 780
175	〃	$-(CH_2)_4CH_3$, H	127~ 8	IR 1700, 1590, 1330, 1180, 965, 715
176	〃	$-C(CH_3)_3$, H	106~ 7	IR 1700, 1600, 1510, 950, 760
177	〃	Et, H	115~ 6	IR 1695, 1590, 1190, 950, 780
178	〃	$-(CH_2)_3CH_3$, H	96~ 9	IR 1705, 1590, 1330, 1100, 945
179	〃	$-(CH_2)_5CH_3$, H	113~ 4	IR 1710, 1600, 1330, 1190, 720
180	〃	$-(CH_2)_6CH_3$, H	108~ 9	IR 1710, 1590, 1330, 720

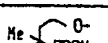
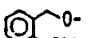
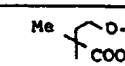
Compound No.	A	R_1, R_2	m.p. (°C)	Physical property values
181	$-CH_2OCH_2-$		-	IR 1685, 1600, 1100, 755 NMR ($CDCl_3$): δ=1.7~2.7(5H,m),3.15(2H,t),4.58(2H,s),4.9(2H,s), 8.4~8.1(9H,m)
182	$-OCH_2-$	〃	120~ 3	IR 1705, 1600, 1250, 1100

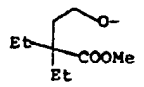
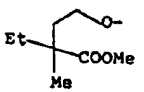
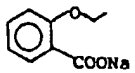
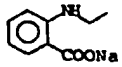
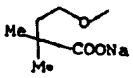
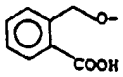
Table 2-9



Compound No.	W	R_1, R_2	m.p. (°C)	Physical Property values	Anti-SRS action [minimum effective conc. (M)]
197	$EtOOC(CH_2)_4$-	C_6H_5,H	78~ 9	IR 1720, 1480, 1180, 860, 740	
199	〃	Me, Me	–	IR 1720, 1540, 1440, 1175, 850, 780 NMR($CDCl_3$): δ=1.25(3H,t), 1.5~1.9(4H,m),2.3(s,6H), 2.2~2.8(m,4H), 4.1(2H,q),6.9~7.4(6H,m)	
200	$EtOOCCH_2NH$-		121~ 4	IR 1720, 1600, 1220, 950, 758	
201	$EtOOC(CH_2)_4NH$-	〃	100~ 9	IR 1710, 1595, 1180, 750	
202	〃	C_6H_5,H	110~ 1	IR 1710, 1595, 1470, 1185, 720	
203	$EtOOC(CH_2)_3NH$-	Me, Me	–	IR 1710, 1595, 1480, 1200, 1190, 755 NMR ($CDCl_3$): δ=1.25(3H,t),2.03(2H,m),2.35(6H,s),2.25~2.50(2H,m), 3.20(2H,m),4.16(2H,q),6.28~7.33(6H,m)	
204	$EtOOC(CH_2)_3NH$-	C_6H_5,H	89.5~ 90	NMR($CDCl_3$) : δ=1.25(3H,t),1.78~2.48(4H,m),3.20(2H,m),4.13(2H,q), 6.38~8.00(12H,m)	
207	$EtOOC(CH_2)_3O$-		135~ 7	IR 1720, 1590, 1273, 1190, 770	
208	$EtOOC(CH_2)_4O$-	〃	72~ 3	IR 1720, 1590, 1180, 870, 755	
209	$EtOOC(CH_2)_3O$-	C_6H_5,H	85~ 86	IR 1725, 1265, 1180, 945, 730	

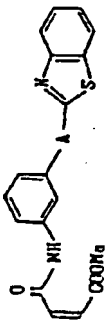
Compound No.	W	R_1, R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]
210			–	IR 1720, 1570, 1140, 950, 760	
211		〃	–	NMR($CDCl_3$) : δ = 0.72~2.97(10H,m), 3.62(3H,s), 3.40~4.21(2H,m), 6.62~7.99(10H,m) IR 1720, 1570, 1145, 950, 760	
212		〃	87~ 8	NMR(CCl_4): δ = 1.26(6H,s), 1.98(2H,t), 3.62(3H,s), 3.92(2H,t), 6.55~7.95(10H,m) IR 1710, 1570, 1260, 1040, 740	
373	$NaOOC(CH_2)_4NH$-	〃	239~ 40	IR 2925, 1560, 1430, 1310, 955, 750	
374	〃	C_6H_5-, H	270~ 1	IR 2825, 1580, 1430, 980, 730	2×10^{-7}
375			215~ 8	IR 1570, 1510, 1380, 1280, 750	2×10^{-7}
394	$NaOOC(CH_2)_2O$-	〃	230~ 41 (decomposition)	IR 1570, 1420, 1200, 950, 750	
395	$NaOOC(CH_2)_3O$-	〃	255~ 8	IR 1550, 1420, 1170, 940, 750	5×10^{-7}
397	$NaOOCCH_2NH$-	〃	257~ 60	IR 1595, 1570, 1410, 940, 745	
398	$NaOOC(CH_2)_4NH$-	〃	239~ 40	IR 1595, 1555, 1430, 955, 750	
399	〃	C_6H_5-, H	270~ 1	IR 1600, 1560, 1430, 960, 730	
401	$NaOOCCH_2O$-		>320	IR 1590, 1425, 940, 745	
402	$NaOOC(CH_2)_3O$-	〃	260~ 2	IR 1550, 1420, 940, 750	

Compound No.	W	R_1, R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]
403	$NaOOC(CH_2)_3O-$	C_6H_5-, H	209~ 90	IR 1545, 1415, 950, 730	
404	$NaOOC(CH_2)_4O-$		216~ 9	IR 1560, 1430, 1270, 750	
405		〃	230 (decomposition)	IR 2920, 1620, 1580, 1440, 750	
406		〃	198~203	IR 1575, 1520, 1480, 1445, 1165, 950, 760	
407		〃	250 (decomposition)	IR 1545, 1400, 1200, 1030, 740	5×10^{-8}
409	$NaOOC(CH_2)_3-$	〃	>350	IR 1615, 1425, 1345, 1090, 1070, 823	
410	$NaOOC(CH_2)_4-$	〃	227~ 30	IR 1560, 1410, 945, 750	
411	$NaOOC(CH_2)_5-$	〃	270~ 82	IR 1560, 1430, 1310, 950, 750	10^{-8}
412	$NaOOC(CH_2)_4-$	C_6H_5-, H	205~ 6	IR 1550, 1440, 960, 730	
413	〃	Me, Me	205~ 90	IR 1580, 1410, 950, 785	
431		$-CH(CH_3)_2$, H	oil	NMR($CDCl_3$): δ = 1.4(6H,s), 1.45(6H,d), 1.4(3H,t), 2.15(2H,t), 2.9~3.4(1H,m), 3.95~4.42(4H,m), 6.7~7.42(7H,m) IR 1720, 1590, 1260, 1145, 1020	

Compound No.	W	R_1, R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc. (M)]
432		$-CH(CH_3)_2$, H	oil	NMR($CDCl_3$): δ=1.33(6H, d), 1.69(4H, q), 1.85(6H, t), 2.07(2H, t), 2.80~3.40(1H, m), 3.65(3H, s), 3.92(2H, t), 6.66 ~ 7.35(7H, m) IR 1720, 1590, 1240, 1140, 1040	
433		"	oil	NMR($CDCl_3$): δ=0.66 ~ 1.12(6H, m), 1.3 ~ 1.9(4H, m), 1.95 ~ 2.30(2H, t), 3.67(3H, s), 3.7 ~ 4.28(2H, m), 6.69 ~ 8.10(10H, m) IR 1720, 1240, 1140, 1030, 760	
434		"	>300	IR 1580, 1380, 1210, 945, 750	2×10^{-8}
435		"	287 ~ 8	IR 1610, 1505, 1380, 950, 750	10^{-7}
436		"	198 ~ 203	IR 1575, 1520, 1445, 1040, 760	10^{-8}
438		$-CH(CH_3)_2$, H	179 ~ 81	IR 1690, 1565, 1265, 1025, 965	

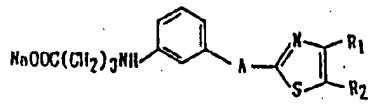
Compound No.	W	R_1 , R_2	m.p. (°C)	Physical property values	Anti-SRS action [minimum effective conc (M)]
439		$-CH(CH_3)_2$, H	106 ~ 8	IR 1690, 1590, 1220, 965, 780	2×10^{-9}
440		"	oil	NMR($CDCl_3$): δ=0.92(6H, t), 1.35(6H, d), 1.82(4H, q), 2.9 ~ 3.6(1H, m), 3.35(2H, s), 6.4 ~ 7.34(7H, m) IR 1685, 1590, 1250, 950, 770	
441			129 ~ 30	IR 1680, 1585, 1440, 1210, 750	5×10^{-8}
442		"	95 ~ 6	IR 1665, 1570, 1280, 1200, 950	
443		$-(CH_2)_2CH_3$, H	64 ~ 5	IR 1690, 1440, 1260, 955	
444		$-CH(CH_3)_2$, H	104 ~ 5	IR 1700, 1260, 1200, 1150, 960	

Table 2-10



Compound No.	A	m.p. (°C)	Physical property values (IR)	Anti-SRS action (minimum effective conc. (M))
368	$-OCH_2-$	115~ 7	1660, 1560, 1440, 750	10^{-7}
369	$-CH_2OCH_2-$	67~ 70	1570, 1440, 1355, 750	10^{-6}
370	$-CONH-$	277~ 80	1665, 1540, 1435, 1275, 745	
371	$-CH=CH-CONH-$	341~ 4	1670, 1545, 1435, 1260, 1070, 745	
372	$-NHCH_2-$	134~ 8	1660, 1560, 1430, 1305, 850, 735	

Table 2-11



Compound No.	A	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SkS action [minimum effective conc. (M)]
376	$-(CH_2)_2-$		148~ 50	2000, 1600, 1550, 1430, 1100, 760	5×10^{-9}
377	-CH=CH-	Me, Me	133~ 5	1600, 1555, 1410, 950, 770	2×10^{-9}
378	〃		170~ 82	1560, 1400, 1305, 940, 770	
379	〃		187~ 70	1625, 1540, 1405, 940, 775	
380	〃	 , H	237~ 8	1560, 1410, 1100, 958, 830, 745	
381	〃	 , H	205~ 7	1560, 1420, 950, 740, 690	
382	〃	Et, Me	144~ 6	1540, 1410, 1330, 950, 765	
383	〃	$-CH(CH_3)_2$, H	125~ 8	1560, 1400, 1300, 940, 765	
384	〃	$-(CH_2)_4CH_3$, H	165~ 70	1625, 1550, 1405, 950, 768	
385	〃	$-(CH_2)_2CH_3$, Et	154~ 5	1555, 1430, 950, 705	

Compound No.	A	R_1, R_2	m.p. (°C)	Physical property values (IR)	Anti-SRS action [minimum effective conc. (M)]
386	-CH=CH-	$-C(CH_3)_3$, H	155~ 7	1560, 1410, 1100, 850, 745	
387	〃	Et, H	138~ 40	1550, 1410, 850, 765	10^{-8}
388	〃	$-(CH_2)_2CH_3$, H	133~ 5	1555, 1410, 853, 770, 685	
389	〃	$-(CH_2)_3CH_3$, H	123~ 7	1595, 1560, 1435, 1410, 955, 770	10^{-7}
390	〃	$-(CH_2)_5CH_3$, H	112~ 5	1560, 1410, 850, 770, 685	
391	〃	$-(CH_2)_6CH_3$, H	153~ 4	1550, 1410, 850, 770	
392	-OCH$_2$-		125~ 30	1615, 1570, 1210, 753	
393	-CH$_2$OCH$_2$-	〃	138~ 45	1675, 1600, 1560, 1400, 755	
400	-CH=CH-	C_6H_5-, H	270~ 6	1600, 1550, 1430, 955, 730	

Table 2-12

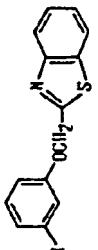
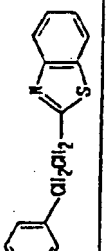
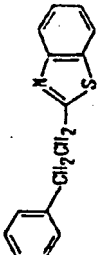
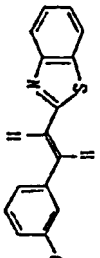
Compound No.	Structural formula	m.p. (°C)	Physical property values (IR)
205		98 ~ 9	1715, 1600, 1250, 1175, 750
408		207 ~ 8	1557, 1430, 1165, 1040, 750
420		221 ~ 5	1680, 1520, 1440, 750
421		108 ~ 8	1570, 1430, 1085, 750

Table 3

Test compound		Anti-SRS action
Compound	Example	[Minimum effective conc. (M)]
1	1	5×10^{-8}
189	9	10^{-6}
199	13	2×10^{-7}
213	17	5×10^{-8}
396	19	2×10^{-7}
414	21	10^{-6}
422	23	10^{-6}
423	24	10^{-6}
424	25	5×10^{-7}
426	27	2×10^{-7}

Table 4

Test Compound		Airway resistance increase inhibition (%)
Compound No.	Dosage (mg/kg)	
213	30	51
223	3	87
227	3	71
272	10	37
297	10	62
353	30	79
396	3	55

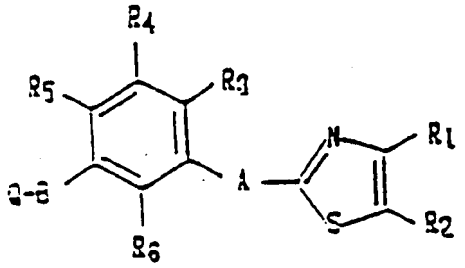
Table 5

Compound No.	Acute toxicity value (LD_{50} mg/kg)
2	> 3000
26	> 3000
213	> 3000
216	> 3000
232	3000
247	> 3000
248	> 3000
249	1000 ~ 2000
281	> 3000
300	1000 ~ 2000
303	2000
313	1560
314	2000 ~ 3000
315	1000 ~ 2000
317	1032
324	1360
325	2000

Compound No.	Acute toxicity value (LD_{50} mg/kg)
326	> 3000
353	3308
355	1928
382	1928
396	2000 ~ 3000
418	> 3000

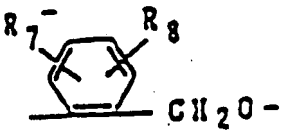
Claims

1. A thiazole derivative represented by the following formula and a pharmaceutically acceptable salt thereof:

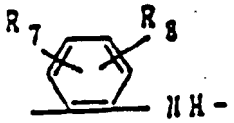


wherein R_1 and R_2 each independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or a phenyl group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group of 1 to 3 carbon atoms or cooperatively represent a tetramethylene group corresponding to a fused cyclohexane ring or a butadienylene group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group having 1 to 3 carbon atoms corresponding to a fused benzene ring; R_3, R_4, R_5 and R_6 each independently represent a hydrogen atom, a hydroxyl group, a lower alkoxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 3 carbon atoms or a halogen atom; A is a linking group selected from the group consisting of -CH=CH-, $-CH_2CH_2-$ $-OCH_2$, $-NHCH_2-$, -CONH-, -CH=CHCONH and $-CH_2OCH_2-$,
B is a group selected from the group consisting of:
$-(CH_2)_n$-CONH-, wherein n is an integer of 0-3,
$-(CH_2)_n$-NH-, wherein n is an integer of 1-4,
$-(CH_2)_n$-0-, wherein n is an integer of 1-4,
$-(CH_2)_n-$, wherein n is an integer of 2-5,

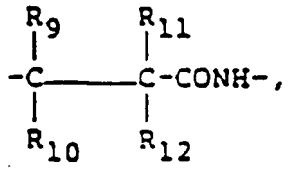
wherein R_7 and R_8 each independently represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms as defined above,



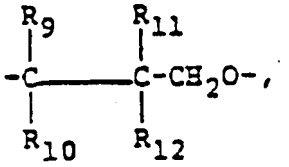
wherein R_7 and R_8 have the same meanings as defined above,



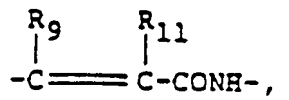
wherein R_7 and R_8 have the same meanings as defined above,



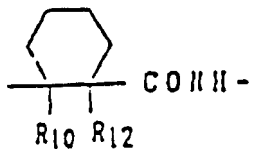
wherein R_9, R_{10}, R_{11} and R_{12} each independently represent a hydrogen atom, a phenyl group or an alkyl group having 1 to 6 carbon atoms,



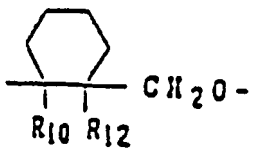
wherein R_9, R_{10}, R_{11} and R_{12} have the same meanings as defined above,



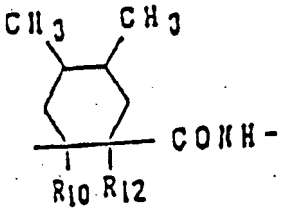
wherein R_9 and R_{11} have the same meanings as defined above,



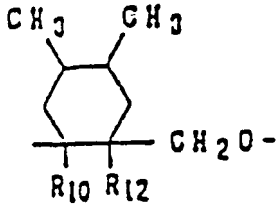
wherein R_{10} and R_{12} have the same meanings as defined above,



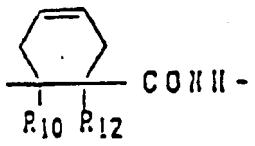
wherein R_{10} and R_{12} have the same meanings as defined above,



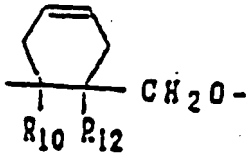
wherein R_{10} and R_{12} have the same meanings as defined above,



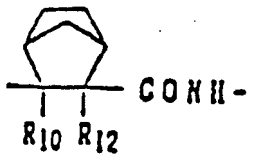
wherein R_{10} and R_{12} have the same meanings as defined above,



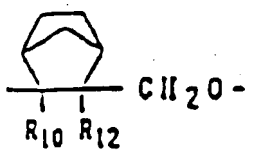
wherein R_{10} and R_{12} have the same meanings as defined above,



wherein R_{10} and R_{12} have the same meanings as defined above,

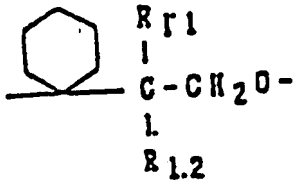


wherein R_{10} and R_{12} have the same meanings as defined above,



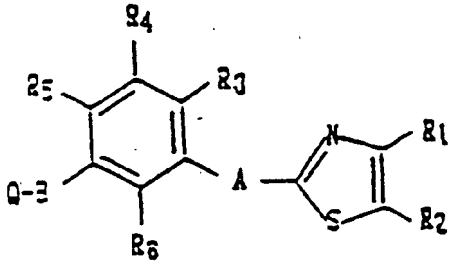
wherein R_{10} and R_{12} have the same meanings as defined above,

wherein R_{11} and R_{12} have the same meanings as defined above, and



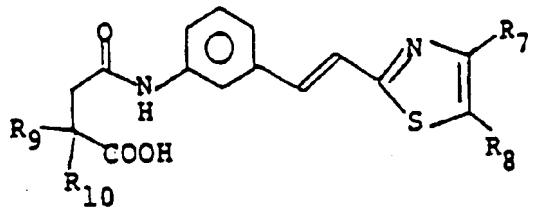
wherein R_{11} and R_{12} have the same meanings as defined above and Q represents a carboxyl group, a lower alkoxy group having 1 to 3 carbon atoms, a hydroxyl group, an alkoxycarbonyl group having 2 to 6 carbon atoms or a 5-tetrazolyl group.

2. A leukotriene antagonist comprising a thiazole derivative represented by the following formula or a pharmaceutically acceptable salt thereof as the active ingredient:



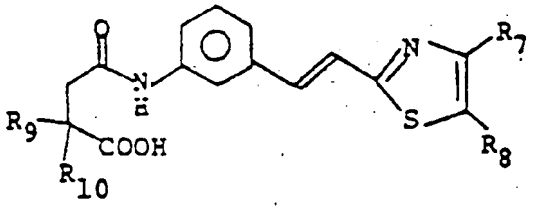
wherein R_1, R_2, R_3, R_4, R_5, R_6 A, B and Q are defined in Claim 1.

3. A thiazole derivative and the pharmaceutically acceptable salt thereof according to Claim 1 represented by the following formula:



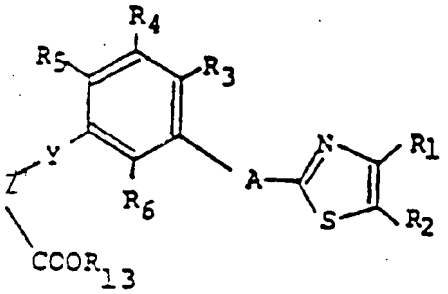
wherein R_7 and R_8 each independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms or cooperatively represent a butadienylene group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group having 1 to 3 carbon atoms corresponding to a fused benzene ring; R_9 and R_{10} each independently represent a hydrogen atom or an alkyl group having 1 to 6 carbon atoms.

4. A leukotriene antagonist comprising a thiazole derivative represented by the following formula or a pharmaceutically acceptable salt thereof according to Claim 2 as the active ingredient:

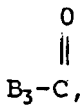


wherein R_7, R_8, R_9, R_{10}, are defined in Claim 3.

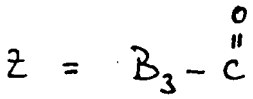
5. A process for preparing a thiazole derivative represented by the formula:



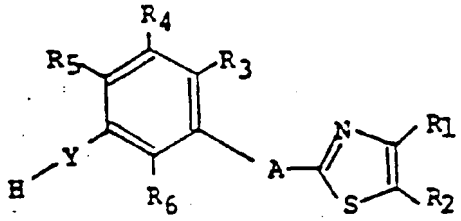
wherein R_1 and R_2 each independently represent a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or a phenyl group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group of 1 to 3 carbon atoms or cooperatively represent a tetramethylene group corresponding to a fused cyclohexane ring or a butadienylene group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group having 1 to 3 carbon atoms corresponding to a fused benzene ring; R_3, R_4, R_5 and R_6 each independently represent a hydrogen atom, a hydroxyl group, a lower alkoxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 3 carbon atoms or a halogen atom; R_{13} represents an alkyl group having 1 to 5 carbon atoms; A is a linking group selected from group consisting of -CH=CH-, $-CH_2CH_2-$ $-OCH_2-$, $-NHCH_2-$, -CONH-, -CH=CHCONH and $-CH_2OCH_2-$, Z represents B_4 or



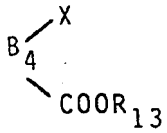
wherein B_4 represents a linking group having 1 to 4 carbon atoms and B_3 represents a direct bond or a linking group having 1 to 3 carbon atoms with the proviso that if



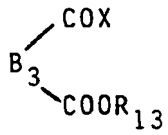
than Y = NH; Y represents oxygen or -NH or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula:



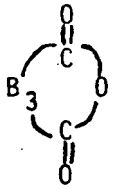
wherein R_1, R_2, R_3, R_4, R_5, R_6, A and Y are the same as defined above, with a compound selected from the group of the following (I)-(K) formulae:



(I)



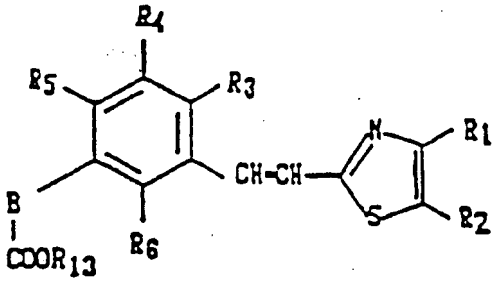
(J)



(K)

wherein X is a halogen atom, B_3 and B_4, are the same as defined above with the proviso that B_3 is not a direct bond in formula (K) and (J) and (K) can be optionally subjected further to hydrolysis to obtain an acid salt and (I) and (J) can be optionally subjected further to esterification.

6. A process for preparing a thiazole derivative represented by the formula:



wherein R_1 and R_2 each independently represent a hydrogen atom, an alky group having 1 to 8 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or a phenyl group or cooperatively represent a tetramethylene group corresponding to a fused cyclohexane ring or a butadienylene group which is unsubstituted or substituted with a halogen atom, a lower alkoxy group having 1 to 3 carbon atoms, a lower alkoxycarbonyl group having 2 to 4 carbon atoms or an alkyl group having 1 to 3 carbon atoms corresponding to a fused benzene ring; R_3, R_4, R_5 and R_6 each independently represent a hydrogen atom, a hydroxyl group, a lower alkoxy group having 1 to 3 carbon atoms, a alkyl group having 1 to 3 carbon atoms or a halogen atom; R_{13} represents an alkyl group having 1 to 5 carbon atoms;

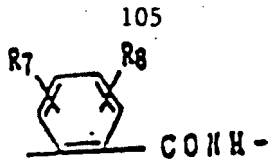
B is a group selected from the group consisting of:

$-(CH_2)_n-CONH-$, wherein n is an integer of 0-3,

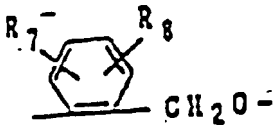
$-(CH_2)_n-NH-$, wherein n is an integer of 1-4,

$-(CH_2)_n-O-$, wherein n is an integer of 1-4,

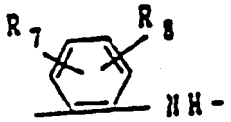
$-(CH_2)_n-$, wherein n is an integer of 2-5,



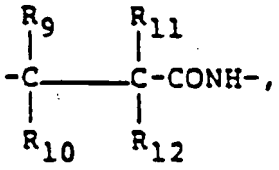
wherein R_7 and R_8 each independently represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms as defined above,



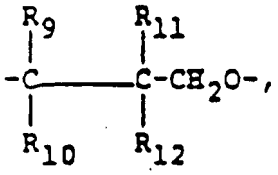
wherein R_7 and R_8 have the same meanings as defined above,



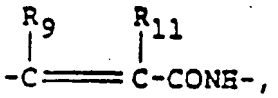
wherein R_7 and R_8 have the same meanings as defined above,



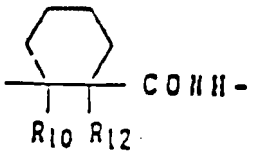
wherein R_9, R_{10}, R_{11} and R_{12} each independently represent a hydrogen atom, a phenyl group or an alkyl group having 1 to 6 carbon atoms,



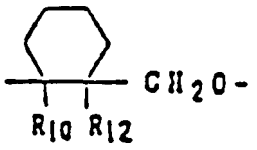
wherein R_9, R_{10}, R_{11} and R_{12} have the same meanings as defined above,



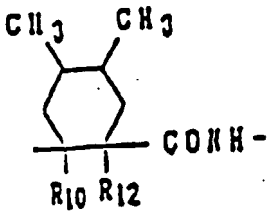
wherein R_9 and R_{11} have the same meanings as defined above,



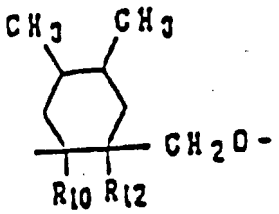
wherein R_{10} and R_{12} have the same meanings as defined above,



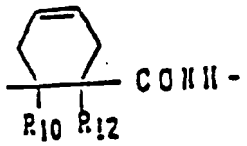
wherein R_{10} and R_{12} have the same meanings as defined above,



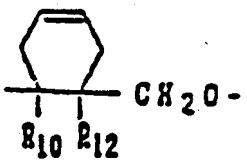
wherein R_{10} and R_{12} have the same meanings as defined above,



wherein R_{10} and R_{12} have the same meanings as defined above,

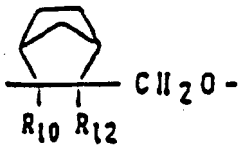


wherein R_{10} and R_{12} have the same meanings as defined above,



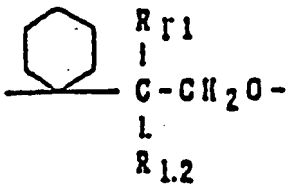
wherein R_{10} and R_{12} have the same meanings as defined above,

wherein R_{10} and R_{12} have the same meanings as defined above,

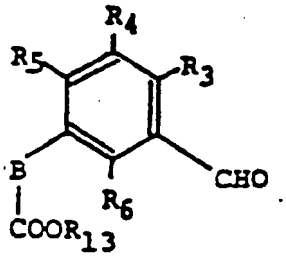


wherein R_{10} and R_{12} have the same meanings as defined above,

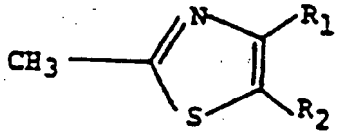
wherein R_{11} and R_{12} have the same meanings as defined above, and



or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula:



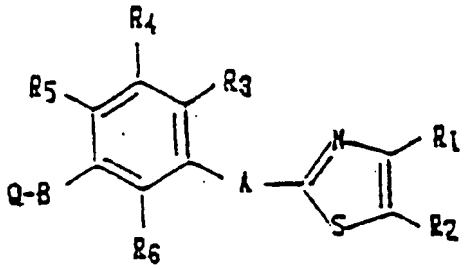
wherein R_3, R_4, R_5, R_6, R_{13} and B are the same as defined above, with a compound represented by the formula:



wherein R_1 and R_2 are the same as defined above, and optionally subjecting further the thus obtained product to hydrolysis to obtain an acid or salt

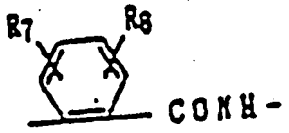
Patentansprüche

1. Thiazolderivat, dargestellt durch die folgende Formel und eines ihrer pharmazeutisch zulässigen Salze:

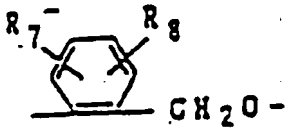


worin R_1 und R_2 jeweils unabhängig ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder eine Phenylgruppe, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, darstellen, oder gemeinsam eine Tetramethylengruppe darstellen, was einem anelierten Cyclohexanring entspricht, oder eine Butadienylengruppe darstellen, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, was einem anellierten Benzolring entspricht; R_3, R_4, R_5 und R_6 jeweils

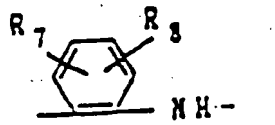
unabhängig ein Wasserstoffatom, eine Hydroxylgruppe, eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen oder ein Halogenatom darstellen; A eine verbindende Gruppe ist, ausgewählt aus der Gruppe, bestehend aus -CH=CH-, $-CH_2CH_2-$, $-OCH_2-$, $-NHCH_2-$, -CONH-, -CH=CHCONH und $-CH_2OCH_2-$, B eine Gruppe ist, die ausgewählt ist aus der Gruppe, bestehend aus: $-(CH_2)_n$-CONH-, wobei n eine ganze Zahl von 0 bis 3 ist, $-(CH_2)_n$-NH-, wobei n eine ganze Zahl von 1 bis 4 ist, $-(CH_2)_n$-O-, wobei n eine ganze Zahl von 1 bis 4 ist, $-(CH_2)_n-$, wobei n eine ganze Zahl von 2 bis 5 ist,



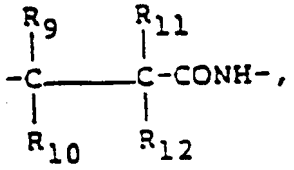
worin R_7 und R_8 jeweils unabhängig ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, wie oben definiert, darstellen,



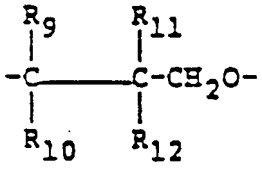
worin R_7 und R_8 dieselben Bedeutungen wie oben haben,



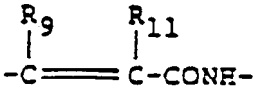
worin R_7 und R_8 dieselben Bedeutungen wie oben haben,



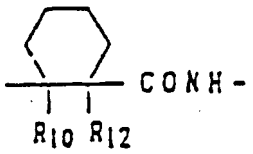
worin R_9, R_{10}, R_{11} und R_{12} jeweils unabhängig ein Wasserstoffatom, eine Phenylgruppe oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen darstellen



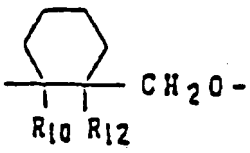
worin R_9, R_{10}, R_{11} und R_{12} dieselben Bedeutungen, wie oben definiert, haben,



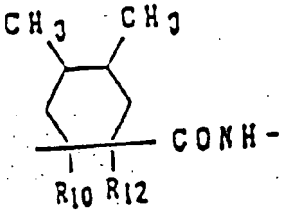
worin R_9 und R_{11} dieselben Bedeutungen wie oben haben,



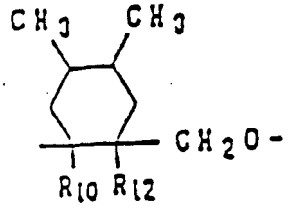
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



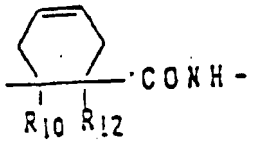
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



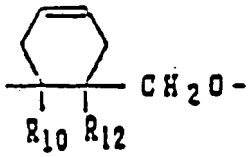
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

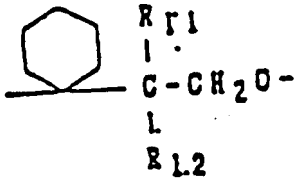


worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

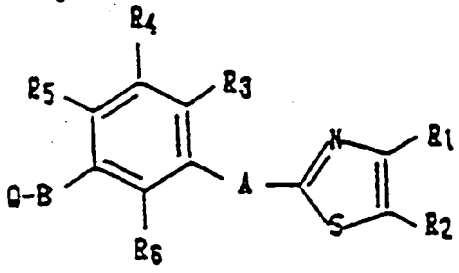
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

worin R_{11} und R_{12} dieselben Bedeutungen wie oben haben, und



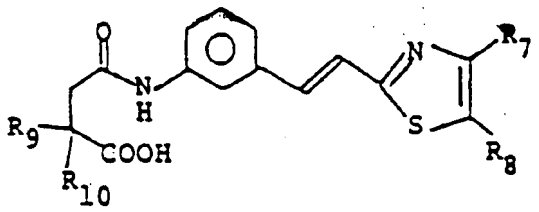
worin R_{11} und R_{12} dieselben Bedeutungen wie oben haben und Q eine Carboxylgruppe, eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, eine Hydroxylgruppe, eine Alkoxycarbonylgruppe mit 2 bis 6 Kohlenstoffatomen oder eine 5-Tetrazolylgruppe darstellt.

2. Ein Leukotrien-Antagonist, umfassend ein Thiazolderivat, dargestellt durch die folgende Formel, oder eines ihrer pharmazeutisch zulässigen Salze als aktiven Bestandteil:



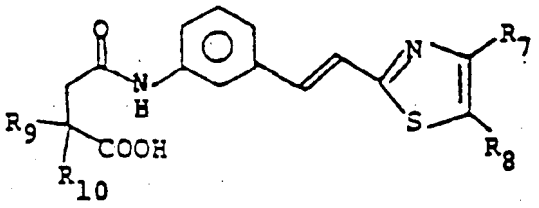
worin R_1, R_2, R_3, R_4, R_5, R_6, A, B und Q wie in Anspruch 1 definiert sind.

3. Thiazolderivat und ihre pharmazeutisch zulässigen Salze gemäss Anspruch 1, dargestellt durch die folgende Formel:



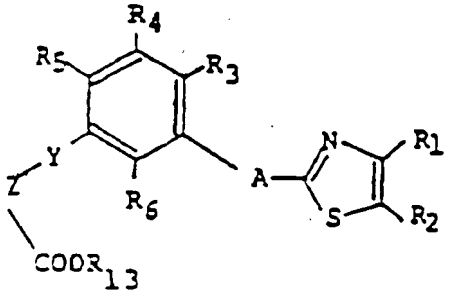
worin R_7 und R_8 jeweils unabhängig ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen darstellen oder zusammen eine Butadienylengruppe darstellen, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, was einem anellierten Benzolring entspricht; R_9 und R_{10} jeweils unabhängig ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen darstellen.

4. Leukotrien-Antagonist, umfassend ein durch die folgende Formel dargestelltes Thiazolderivat oder eines seiner pharmazeutisch zulässigen Salze gemäss Anspruch 2, als aktiven Bestandteil:



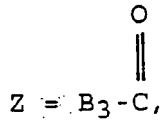
worin R_7, R_8, R_9 und R_{10} in Anspruch 3 definiert sind.

5. Verfahren zur Herstellung eines Thiazolderivats, dargestellt durch die Formel:

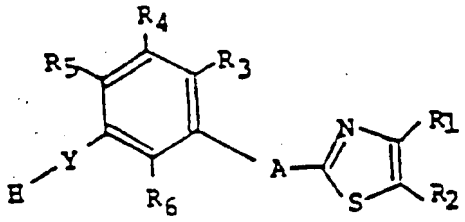


worin R_1 und R_2 jeweils unabhängig ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen, oder eine Phenylgruppe, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, darstellen oder gemeinsam eine Tetramethylengruppe darstellen, was einem anellierten Cyclohexanring entspricht, oder eine Butadienylengruppe darstellen, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, was einem anellierten Benzolring entspricht; R_3, R_4, R_5 und R_6 jeweils unabhängig ein Wasserstoffatom, eine Hydroxylgruppe, eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen oder ein Halogenatom darstellen; R_{13} eine Alkylgruppe mit 1 bis 5 Kohlenstoffatom darstellt; A eine verbindende Gruppe ist, die ausgewählt ist aus der Gruppe, bestehend aus -CH=CH-, $-CH_2CH_2-$, $-OCH_2-$, $-NHCH_2-$, -CONH-, -CH=CHCONH und $-CH_2OCH_2-$; Z B_4 oder

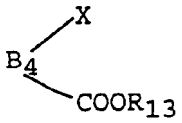
darstellt, wobei B_4 eine verbindende Gruppe mit 1 bis 4 Kohlenstoffatomen darstellt und B_3 eine direkte Bindung oder eine verbindende Gruppe mit 1 bis 3 Kohlenstoffatomen darstellt, mit der Massgabe, dass, wenn



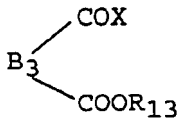
dann Y = NH ist, Y Sauerstoff oder -NH darstellt oder eines seiner pharmazeutisch zulässigen Salze, umfassend die Umsetzung einer Verbindung, dargestellt durch die Formel:



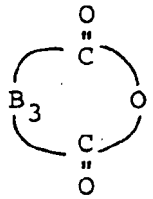
worin R_1, R_2, R_3, R_4, R_5, R_6, A und Y wie oben definiert sind, mit einer Verbindung, ausgewählt aus der Gruppe der folgenden Formeln (I) bis (K):



(I)



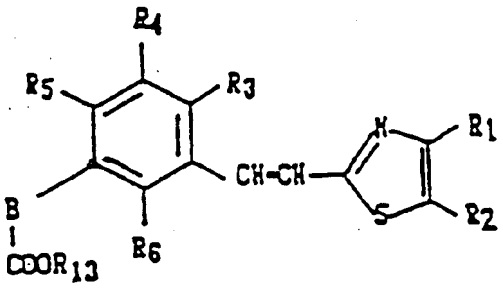
(J)



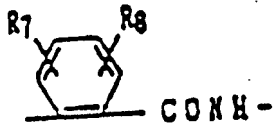
(K)

worin X ein Halogenatom ist, B_3 und B_4 wie oben definiert sind, mit der Massgabe, dass B_3 keine direkte Bindung in Formel (K) ist, und (J) und (K) wahlweise weiterhin der Hydrolyse unterworfen werden können, so dass ein Säuresalz erhalten wird, und (I) und (J) wahlweise weiterhin der Veresterung unterworfen werden können.

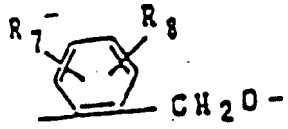
6. Verfahren zur Herstellung eines Thiazolderivats, dargestellt durch die Formel



worin R_1 und R_2 jeweils unabhängig ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen, oder eine Phenylgruppe darstellen oder gemeinsam eine Tetramethylengruppe darstellen, was einem anellierten Cyclohexanring entspricht, oder eine Butadienylengruppe darstellen, die unsubstituiert oder substituiert mit einem Halogenatom, einer Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, einer Niederalkoxycarbonylgruppe mit 2 bis 4 Kohlenstoffatomen oder einer Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, was einem anellierten Benzolring entspricht; R_3, R_4, R_5 und R_6 jeweils unabhängig ein Wasserstoffatom, eine Hydroxylgruppe, eine Niederalkoxygruppe mit 1 bis 3 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen oder ein Halogenatom darstellen; R_{13} eine Alkylgruppe mit 1 bis 5 Kohlenstoffatomen darstellt;
B eine Gruppe ist, die ausgewählt ist aus der Gruppe, bestehend aus: $-(CH_2)_n$-CONH-, wobei n eine ganze Zahl von 0 bis 3 ist, $-(CH_2)_n$-NH-, wobei n eine ganze Zahl von 1 bis 4 ist, $-(CH_2)_n$-O-, wobei n eine ganze Zahl von 1 bis 4 ist, $-(CH_2)_n$-, wobei n eine ganze Zahl von 2 bis 5 ist,

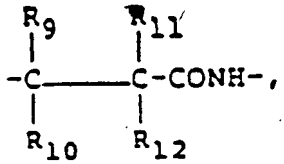


worin R_7 und R_8 jeweils unabhängig ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, wie oben definiert, darstellen,



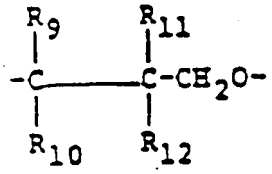
worin R_7 und R_8 dieselben Bedeutungen wie oben haben,

worin R_7 und R_8 dieselben Bedeutungen wie oben haben,

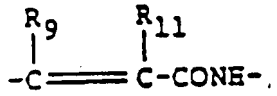


worin R_9, R_{10}, R_{11} und R_{12} jeweils unabhängig ein Wasserstoffatom, eine Phenylgruppe oder eine

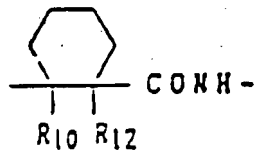
Alkylgruppe mit 1 bis 6 Kohlenstoffatomen darstellen



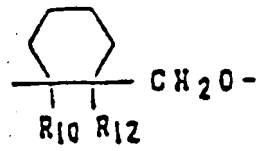
worin R_9, R_{10}, R_{11} und R_{12} dieselben Bedeutungen, wie oben haben,



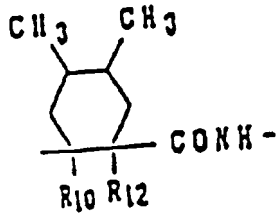
worin R_9 und R_{11} dieselben Bedeutungen wie oben haben,



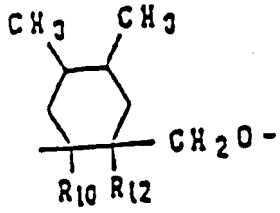
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



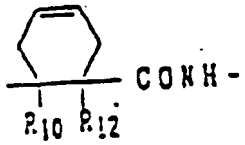
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



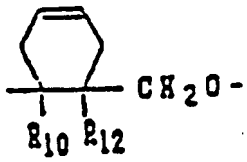
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

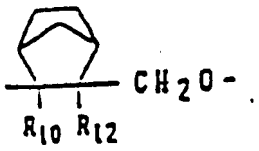


worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

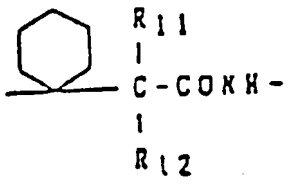


worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,

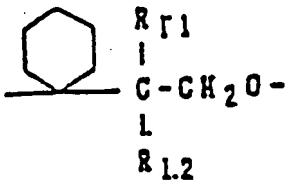
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



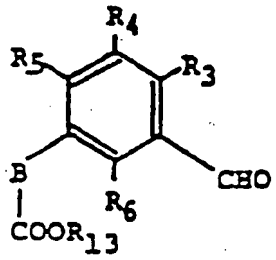
worin R_{10} und R_{12} dieselben Bedeutungen wie oben haben,



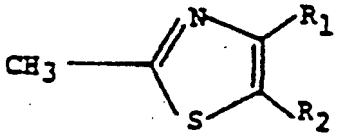
worin R_{11} und R_{12} dieselben Bedeutungen wie oben haben, und



worin R_{11} und R_{12} dieselben Bedeutungen wie oben haben, oder eines seiner pharmazeutisch annehmbaren Salze,
umfassend die Umsetzung einer Verbindung, dargestellt durch die Formel:



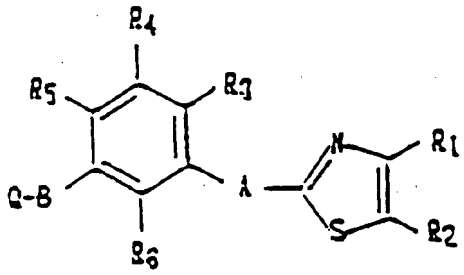
worin R_3, R_4, R_5, R_6, R_{13} und B wie oben definiert sind, mit einer Verbindung, dargestellt durch die Formel:



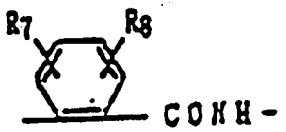
worin R_1 und R_2 wie oben definiert sind, und wahlweise weiterhin Hydrolyse des so erhaltenen Produkts zum Erhalt einer Säure oder eines Salzes.

Revendications

1. Dérivé du thiazole représenté par la formule suivante, et ses sels pharmaceutiquement acceptables:

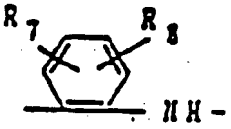


dans laquelle R_1 et R_2 représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe phényle qui est insubstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle de 1 à 3 atomes de carbone, ou représentent ensemble un groupe tétraméthylène correspondant à un noyau cyclohexane fusionné ou un groupe butadiénylène qui est insubstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle ayant 1 à 3 atomes de carbone correspondant à un noyau benzène fusionné; R_3, R_4, R_5 et R_6 représentent chacun indépendamment un atome d'hydrogène, un groupe hydroxyle, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alkyle ayant 1 à 3 atomes de carbone ou un atome d'halogène;
A est un groupe de liaison choisi dans le groupe constitué par $-CH=CH-$, $-CH_2CH_2-$, $-OCH_2-$, $-NHCH_2-$, $-CONH-$, $-CH=CHCONH$, et $-CH_2OCH_2-$,
B est un groupe choisi dans le groupe constitué par :
$-(CH_2)_n-CONH-$ où n est un entier de 0 à 3,
$-(CH_2)_n-NH-$ où n est un entier de 1 à 4,
$-(CH_2)_n-O-$ où n est un entier de 1 à 4,
$-(CH_2)_n-$ où n est un entier de 2 à 5,

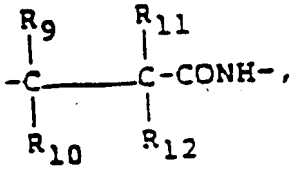


dans laquelle R_7 et R_8 représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone comme défini ci-dessus,

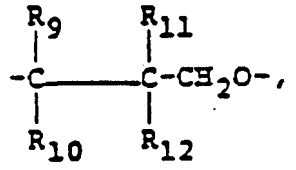
dans laquelle R_7 et R_8 ont les mêmes significations que celles définies ci-dessus,



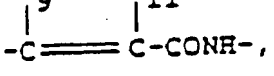
dans laquelle R_7 et R_8 ont les mêmes significations que celles définies ci-dessus,



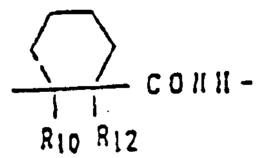
dans laquelle R_9, R_{10}, R_{11} et R_{12} représentent chacun indépendamment un atome d'hydrogène, un groupe phényle ou un groupe alkyle ayant 1 à 6 atomes de carbone,



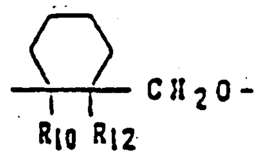
dans laquelle R_9, R_{10}, R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus,



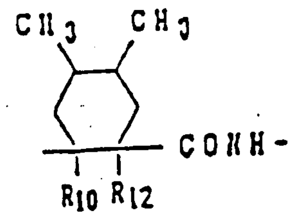
dans laquelle R_9 et R_{11} ont les mêmes significations que celles définies ci-dessus,



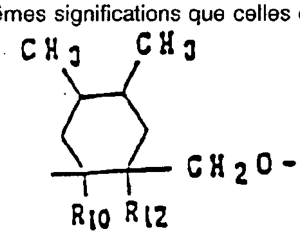
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



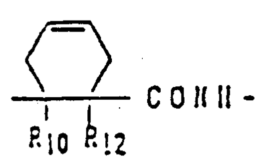
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



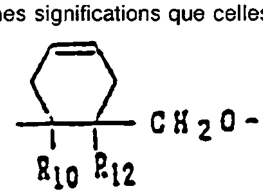
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,

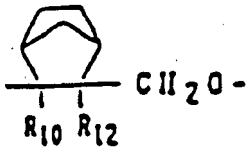


dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,

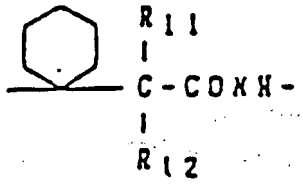


dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,

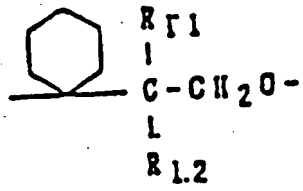
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,

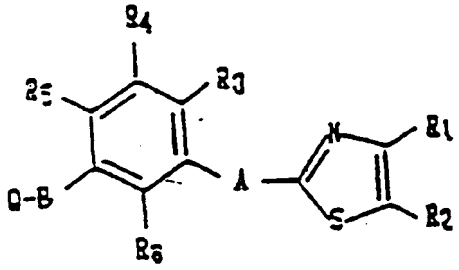


dans laquelle R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus, et



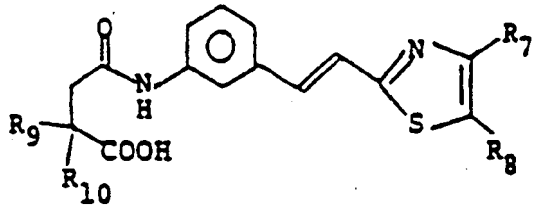
dans laquelle R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus, et Q représente un groupe carboxyle, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe hydroxyle, un groupe alcoxycarbonyle ayant 2 à 6 atomes de carbone ou un groupe 5-tétrazolyle.

2. Antagoniste de leucotriène comprenant un dérivé de thiazole représenté par la formule suivante ou un sel pharmaceutiquement acceptable comme ingrédient actif :



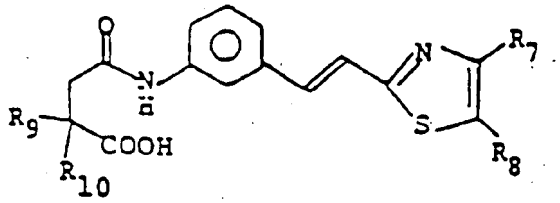
dans laquelle R_1, R_2, R_3, R_4, R_5, R_6, A, B et Q sont définis comme dans la revendication 1.

3. Dérivé du thiazole et ses sels pharmaceutiquement acceptables selon la revendication 1, représenté par la formule suivante



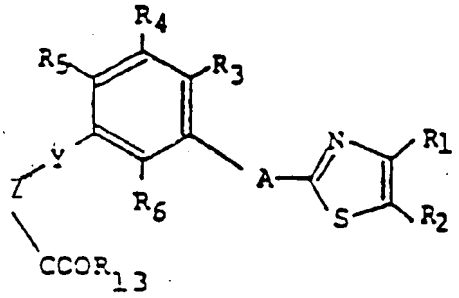
dans laquelle R_7 et R_8 représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant 1 à 8 atomes de carbone ou représentent ensemble un groupe butadiénylène qui est insusbstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle ayant 1 à 3 atomes de carbone correspondant à un noyau benzène fusionné; R_9 et R_{10} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone.

4. Antagoniste de leucotriène comprenant un dérivé du thiazole représenté par la formule suivante ou un sel pharmaceutiquement acceptable selon la revendication 2, comme ingrédient actif :



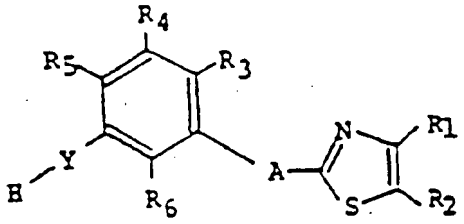
dans laquelle R_7, R_8, R_9 et R_{10} sont définis comme dans la revendication 3.

5. Procédé de préparation d'un dérivé du thiazole représenté par la formule :

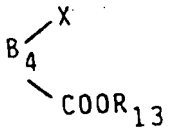


dans laquelle R_1 et R_2 représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe phényle qui est insubstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle de 1 à 3 atomes de carbone, ou représentent ensemble un groupe tétraméthylène correspondant à un noyau cyclohexane fusionné ou un groupe butadiénylène qui est insubstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle ayant 1 à 3 atomes de carbone correspondant à un noyau benzène fusionné; R_3, R_4, R_5 et R_6 représentent chacun indépendamment un atome d'hydrogène, un groupe hydroxyle, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alkyle ayant 1 à 3 atomes de carbone ou un atome d'halogène; R_{13}

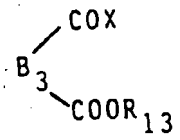
représente un groupe alkyle ayant 1 à 5 atomes de carbone;
A est un groupe de liaison choisi dans le groupe constitué par -CH = CH-, $-CH_2CH_2-$, $-OCH_2-$, $-NHCH_2-$, -CONH-, -CH = CHCONH, et $-CH_2OCH_2-$,
Z représente $-B_4$ ou $-B_3-CO-$ où B_4 représente un groupe de liaison ayant 1 à 4 atomes de carbone, et B_3 représente une liaison directe ou un groupe de liaison ayant 1 à 3 atomes de carbone, avec la réserve que, quand Z = B_3-CO- alors Y = NH; Y représente un oxygène ou -NH, ou ses sels pharmaceutiquement acceptables,
qui consiste à faire réagir un composé représenté par la formule :



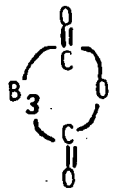
dans laquelle R_1, R_2, R_3, R_4, R_5, R_6, A et Y sont les mêmes que ceux définis ci-dessus, avec un composé choisi dans le groupe des formules (I)-(K) suivantes :



(I)



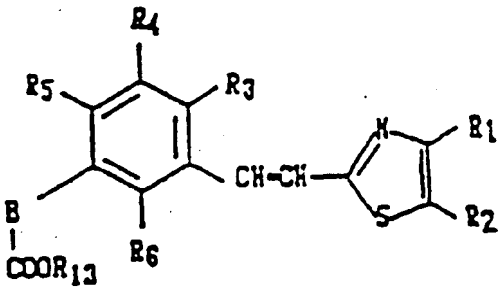
(J)



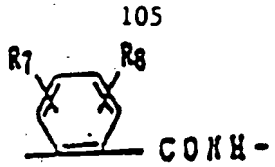
(K)

dans lesquelles X est un atome d'halogène, B_3 et B_4 sont les mêmes que ceux définis ci-dessus, avec la réserve que B_3 n'est pas une liaison directe dans la formule (K), et (J) et (K) peuvent être le cas échéant soumis en outre à une hydrolyse pour obtenir un sel d'acide et (I) et (J) peuvent être le cas échéant soumis en outre à une estérification.

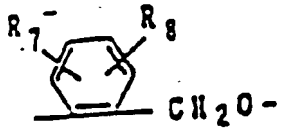
6. Procédé de préparation d'un dérivé du thiazole représenté par la formule :



dans laquelle R_1 et R_2 représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe phényle, ou représentent ensemble un groupe tétraméthylène correspondant à un noyau cyclohexane fusionné ou un groupe butadiénylène qui est insubstitué ou substitué par un atome d'halogène, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alcoxycarbonyle inférieur ayant 2 à 4 atomes de carbone ou un groupe alkyle ayant 1 à 3 atomes de carbone correspondant à un noyau benzène fusionné; R_3, R_4, R_5 et R_6 représentent chacun indépendamment un atome d'hydrogène, un groupe hydroxyle, un groupe alcoxy inférieur ayant 1 à 3 atomes de carbone, un groupe alkyle ayant 1 à 3 atomes de carbone ou un atome d'halogène; R_{13} représente un groupe alkyle ayant 1 à 5 atomes de carbone;
B est un groupe choisi dans le groupe constitué par :
$-(CH_2)_n-CONH-$ où n est un entier de 0 à 3,
$-(CH_2)_n-NH-$ où n est un entier de 1 à 4,
$-(CH_2)_n-O-$ où n est un entier de 1 à 4,
$-(CH_2)_n-$ où n est un entier de 2 à 5,

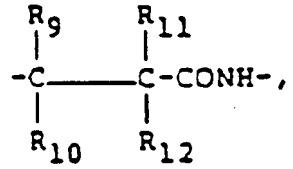


dans laquelle R_7 et R_8 représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone comme défini ci-dessus,

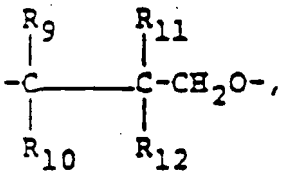


dans laquelle R_7 et R_8 ont les mêmes significations que celles définies ci-dessus,

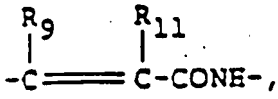
dans laquelle R_7 et R_8 ont les mêmes significations que celles définies ci-dessus,



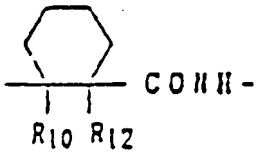
dans laquelle R_9, R_{10}, R_{11} et R_{12} représentent chacun indépendamment un atome d'hydrogène, un groupe phényle ou un groupe alkyle ayant 1 à 6 atomes de carbone,



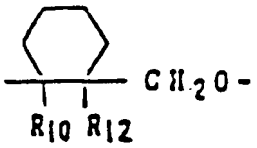
dans laquelle R_9, R_{10}, R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus,



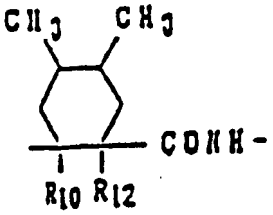
dans laquelle R_9 et R_{11} ont les mêmes significations que celles définies ci-dessus,



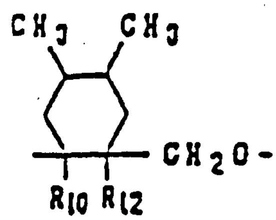
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



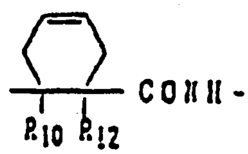
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



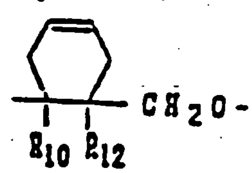
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



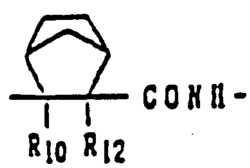
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



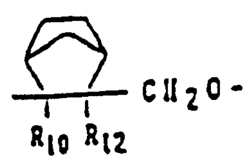
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



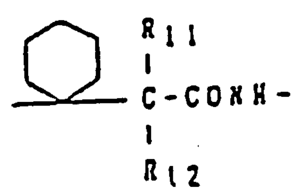
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



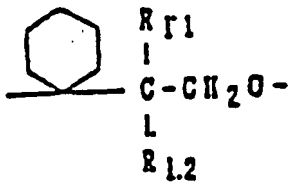
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



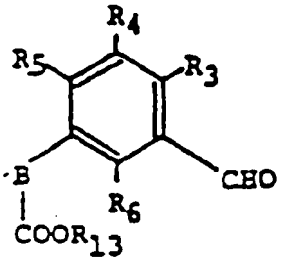
dans laquelle R_{10} et R_{12} ont les mêmes significations que celles définies ci-dessus,



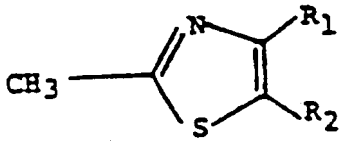
dans laquelle R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus, et



dans laquelle R_{11} et R_{12} ont les mêmes significations que celles définies ci-dessus,
ou un sel pharmaceutiquement acceptable, consistant à faire réagir un composé représenté par la formule :



dans laquelle R_3, R_4, R_5, R_6, R_{13} et B sont les mêmes que ceux définis ci-dessus, avec un composé représenté par la formule :



dans laquelle R_1 et R_2 sont les mêmes que ceux définis ci-dessus, et le cas échéant à soumettre en outre le produit ainsi obtenu à une hydrolyse pour obtenir un acide ou un sel.